

QUANTIFICATION OF RHYTHM AND TIME PATTERN IN REFLEXIVE AND VOLUNTARY EYE MOVEMENTS

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- IV Pyykkö, I. and Dahlen, A.I. 1983. Intrabeat relationship of postrotatory nystagmus in patients with neurological disorders. Acta Otolaryngologica (Stockh). Accepted for publication.

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- VI Pyykkö, I., Dahlen, A.I., Schalén, L. and Hindfelt, B. 1983. Eye movements in patients with speech dyspraxia. Acta Otolaryngologica (Stockh). Accepted for publication.

Contents

1	INTRODUCTION	5
1.1	Introductory remarks	5
1.2	Definitions	5
1.3	Neurophysiological aspects of vestibulo-ocular reflex arch	6
1.3.1	Two-synaptic vestibulo-ocular reflex (VOR) arch	6
1.3.2	Polysynaptic vestibulo-ocular reflex (VOR) arch	6
1.3.3	Neurophysiological aspects of fast phase of nystagmus	7
1.3.4	Exponential model of postrotatory nystagmus response	8
1.4	Dysrhythmia of vestibular nystagmus	8
1.4.1	Dysrhythmia in caloric test	8
1.4.2	Dysrhythmia in rotatory test	9
1.5	Neurophysiological aspects of voluntary eye movements	9
1.5.1	Initiation of voluntary eye movements	9
1.5.2	Parameters of saccades	10
1.5.3	Parameters of smooth pursuit	11
1.6	Purpose of the study	11
2	SUBJECTS AND METHODS	13
2.1	Subjects	13
2.1.1	Normal subjects	13
2.1.2	Patients	14
2.2	Methods	15
2.2.1	Recording of eye movements	15
2.2.2	Test procedure	15
2.2.3	Testing of saccades	16
2.2.4	Testing of tracking eye movements	16
2.2.5	Testing of angular acceleration induced nystagmus	16
2.3	Statistics	17
3	RESULTS	18
3.1	Studies on applicability of exponential model to postrotatory nystagmus variables	18
3.1.1	Normal subjects	18
3.1.2	Patients with neurological disorders	19

3.2	Intrabeat relationship of postrotatory nystagmus	22
3.2.1	Normal subjects	22
3.2.2	Patients with neurological disorders	23
3.3	Oculomotor control in patients with lesions in the frontal lobe	26
4	DISCUSSION	28
4.1	General findings	28
4.2	Comments on the methods	28
4.2.1	Rotatory test	28
4.2.2	Statistical work-up	29
4.2.3	Selection of the patients	30
4.3	What is dysrhythmia of nystagmus?	30
4.4	Comments on suitability of exponential model for dysrhythmia evaluation	31
4.5	Comments on intrabeat relationship of nystagmus	31
4.6	Frontal lobe and eye movements - an unresolved problem?	33
5	CONCLUSIONS	35
6	ACKNOWLEDGEMENTS	37
7	REFERENCES	38

1. Introduction

1.1. Introductory remarks

Eye movements may be voluntary, occur spontaneously or be induced reflexively. In patients with vertigo it is customary to search for spontaneous, gaze and positional nystagmus and also to observe nystagmus induced by various vestibular tests. However, analysis of nystagmus is often not sufficient to reveal a disturbance in the central projections of the vestibular system. Evaluation of voluntary eye movements, e.g. saccades and smooth pursuit, may sometimes be a better way to approach a dysfunction within the "central vestibular system". In otoneurological praxis, measurement of velocity and precision of saccades, and also of smooth pursuit is thus usually complementary to measurement of velocity and duration of different types of nystagmus.

It should be emphasized that the induced nystagmus may exhibit transient changes which do not necessarily influence the velocity or the duration of the response. These deviations in the nystagmus pattern, viz. dysrhythmia of nystagmus, have been recognized in normal subjects as well as in patients with central vestibular lesions. The mechanisms of nystagmic dysrhythmia and its diagnostic significance are still not fully known.

A detailed analysis of dysrhythmia may afford insight into the mechanisms subserving nystagmus and may also help to distinguish a pathological reaction from a normal one. In the present study an effort is made to analyse quantitatively deviations occurring in time, amplitude and the velocity frame during postrotatory nystagmus response and to explore aspects of supratentorial control of nystagmus and voluntary gaze.

1.2. Definitions

Dysrhythmia of nystagmus in the present work denotes all the sudden changes in nystagmus which can occur in time, amplitude, or the velocity frame of a nystagmus beat or a response. Thus, dysrhythmia embraces frequency variations, amplitude variations, velocity variations, pauses, and various combinations.

Peripheral vestibular system in the present report comprises the labyrinth and the vestibular nerve up to the brain stem.

The central vestibular system includes any part of the vestibulo-ocular reflex arch or its control system within the brain stem or elsewhere in the central nervous system (CNS).

Thus the central structures comprise brain stem, including vestibular nuclei, the cerebellum and certain supratentorial structures such as frontal eye field (FEF), posterior parietal association cortex and occipital cortex.

1.3. Neurophysiological aspects of vestibulo-ocular reflex arch

1.3.1. Two-synaptic vestibulo-ocular reflex (VOR) arch

The basic elements of the vestibulo-ocular reflex (VOR) arch consist of the hair cells in the cupula, the afferent neurons of Scarpa's ganglion, interneurons of the vestibular nuclei and motor neurons of the oculomotor nuclei (Tarlov, 1972; Highstein, 1973). One of the output pathways of the VOR arch is mediated via medial longitudinal fasciculus (MLF) (Lorente de N6, 1933). Two other pathways have been outlined anatomically and physiologically, namely one through brachium conjunctivum and one through the ascending tract of Deiter (Highstein & Reisine, 1979). For the horizontal VOR, which originates in the horizontal semicircular canals, the di-synaptic pathway presumably projects through the ascending tract of Deiter to the ipsilateral oculomotor nucleus (Highstein & Reisine, 1979).

Whereas the superior vestibular nucleus mediates inhibitory responses, the medial vestibular nucleus exerts both facilitatory and inhibitory influence on the eye's motor nuclei (Tarlov, 1972; Highstein, 1973). The medial nucleus sends facilitatory inputs to the contralateral abducens nucleus, while concomitantly the superior vestibular nucleus conveys inhibitory impulses to the ipsilateral abducens nucleus and to the contralateral oculomotor nuclei (Ito, 1975).

Furthermore, most of the cells in each of these nuclei respond to vestibular stimulation either by increasing (type I neurons) or decreasing (type II neurons) their resting discharging rate (Duensing & Schaefer, 1959). During unilateral vestibular stimulation, type II cells in the contralateral vestibular nucleus are facilitated by impulses travelling via the commissural pathways (Shimazu, 1972). The eye motor responses will hence be "sharpened". These very same neurons in the vestibular nucleus are presumably driven by inhibitory cerebellar cortical and excitatory cerebellar nuclear inputs via direct vestibulo-cerebellar pathways (Ito, 1975). As a result of vestibular stimulation the eyes start to deviate in a direction opposite for the movement of the head, with a velocity equal to the head's velocity.

1.3.2. Polysynaptic vestibulo-ocular reflex (VOR) arch

Vestibular trajectories outside the two-synaptic VOR arch are still not delineated in detail (cf. Highstein & Reisine, 1979). For polysynaptic VOR arch, brain structures such as pontine reticular formation (PRF) and vestibulo-cerebellum are intimately involved in the vestibular responses (McCabe, 1965;

Cohen et al., 1968; Keller, 1974). Vestibular neurons in the PRF are activated by stimulation of the contralateral labyrinth via commissural fibres (Maeda et al., 1972). Activity linked to type I and II vestibular neurons has been observed in the PRF (Hikosaka et al., 1977). Stimulation- (Keller, 1974) and lesion experiments (Cohen et al., 1968) on PRF in monkey have indicated that the slow phase of nystagmus is dependent on the PRF. The mechanism setting the time frame of various phases of nystagmus is as yet not known in detail (cf. Hepp & Henn, 1979).

Nevertheless, rhythmic activity linked to slow and fast phases of nystagmus, respectively, has been recorded in the vestibular nuclei (Fuchs & Kimm, 1975; Shimazu, 1979). Since a lesion in the PRF abolishes this activity (Jaeger et al., 1981), it is possible that nystagmus is compiled in the PRF and the activity observed in the vestibular nuclei is secondary to that of the PRF (Kaneko et al., 1981). The vestibular nuclei (McCabe, 1965; Hikosaka et al., 1977; Shimazu, 1979), however, may be involved in processing of nystagmus by conveying head velocity signals through the disynaptic VOR arch to the oculomotor nuclei (Highstein & Reisine, 1979). As a result of interaction of the two-synaptic and polysynaptic VOR arch the slow phase of nystagmus will have a definite amplitude and duration and the nystagmus is composed of slow and fast phases.

1.3.3. Neurophysiological aspects of fast phase of nystagmus

Fast phases of nystagmus seem to subserve the orientation reflexes by anticipating the movement of the head and by providing a new fixation point for the eyes. Study of patients with lesions at different sites within the vestibular system supplies some information on possible origin of the fast phase. Henriksson et al. (1981) and Pyykkö et al. (1981) showed that a lesion located in the labyrinth did not reduce the peak velocity of the fast component, whereas a lesion within the brain stem frequently did so. It is remarkable that the peak velocities of various kinds of nystagmus may sometimes be dissociated and that in one and the same patient the peak velocity of the fast phase in one type of nystagmus may be normal, whereas in another type it may be reduced (Pyykkö & Wennmo, 1980; Wennmo & Hindfelt, 1980). Moreover, when degenerative disease involves the posterior fossa, fast phase velocity alone may be reduced (Zee et al., 1976). Similar observations have been made in patients with Huntington's chorea (Starr, 1967). Also, the fast phase seems to be more influenced by pharmacologically active agents than is the slow phase (Blair & Gavin, 1979; Birns & Honrubia, 1980; Furman et al., 1981).

The clinical observations mentioned are consistent with results of single unit recordings (Keller, 1974), stimulation (Keller, 1974) and lesion studies (Cohen et al., 1968), emphasizing the importance of PRF for the origin of the fast phase of nystagmus. The results of clinical and neurophysiological studies indicate that triggering of the fast phase occurs by activation of the neurons in the paramedian part of PRF.

1.3.4. Exponential model of postrotatory nystagmus response

It was originally suggested that stimulation of the semi-circular canal shifts the cupula (Dohlman, 1925; Steinhausen, 1931; van Egmond et al., 1949) and that the maximum extent of the cupular deviation ought to correspond to the maximum value of movement sensation in Bărány's rotatory test. Furthermore, the returning velocity of the cupula was related to the decay of postrotatory responses. These ideas were fundamental in cupulometry (de Wit, 1953). In nystagmus recording the slow phase velocity corresponded well to movement sensation, although it had a rather shorter time constant than was observed in movement sensation (van Egmond & Groen, 1955; Honrubia et al., 1982).

In a mathematical model for cupulometry (van Egmond et al., 1949) the momentary cupular deviation (ξ) was thought to be exponentially related ($\xi = e^{a_1 t + a_2}$) to the returning velocity of the cupula (a_1) at a given time point (t) and to the maximum value of the cupular deviation (a_2). Furthermore, the cupular deviation was related to the velocity of the slow phase of nystagmus (V_1). A linear transfer function was assumed between the cupular deviation and eye velocity, with a transfer coefficient (C); $\xi = C \cdot V_1$. Since the transfer function between cupula and eyes ($C \cdot V_1 = e^{a_1 t + a_2}$) is exponential, it can be visualized on a semilogarithmic scale by plotting nystagmus velocities against time. The values will fall in line. The intercept with the y-axis of the regression line is related to exponential constant a_2 and describes the response maximum. The slope is related to the exponential constant a_1 which indicates the inverted value of the time constant of the slow phase velocity.

Variations in the exponential constants a_1 and a_2 in the postrotatory response were determined and differences between individuals were assumed to indicate hypersensitivity or dysfunction of the VOR (de Wit, 1953).

1.4. Dysrhythmia of vestibular nystagmus

1.4.1. Dysrhythmia in caloric test

Spiegel & Aronson (1933) observed more frequent pauses in nystagmus response among patients with lesions affecting the CNS than in normal subjects. Leidler (1939) extended the definition of dysrhythmia to embrace both the slow and the fast phase of nystagmus and found dysrhythmia predominantly in patients with lesions affecting the CNS. Consistently in many reports, dysrhythmia has been assumed to stem from a lesion within the CNS (Aschan et al., 1956; Riesco-MacClure & Stroud, 1960; Bertrand & Montreuil, 1966). However, Clément (1970) found that even in normal subjects all the main types of dysrhythmia can arise, viz. dysmetria, petit ecriture, salvos, various types of group formation, and secondary phase of nystagmus. According to Clément (1970) the presence or

absence of dysrhythmia can be attributed to the degree of attentiveness of the test subjects.

Hamid et al. (1979) and Hamid & Hinchcliffe (1980) analysed nystagmus components between two successive nystagmus beats during caloric testing - the so-called interbeat interval. When applying this analysis in 20 patients with known neuro-otological disorders, a pathological nystagmus response was observed in 15 of them (Hamid & Hinchcliffe, 1980), whereas conventional analysis of slow-speed velocity of nystagmus revealed abnormalities in only 5 patients. Thus, according to these authors pathological processes affecting the VOR arch appeared more often as irregularities between duration of successive nystagmus beats than as abnormalities in the culmination velocity. These reports do not mention, however, the site of lesion in the patients investigated. Consequently the value of this type of analysis for distinguishing central vestibular disorders from peripheral ones is not yet settled.

1.4.2. Dysrhythmia in rotatory test

Several authors have questioned whether or not the disturbances in the nystagmus amplitude of per- or postrotatory response can reveal a possible disorder in the CNS. Baloh & Honrubia (1979) described several patterns of dysrhythmic nystagmus that may signify a central lesion. According to these authors a dysrhythmic nystagmus of cerebellar origin is disorganized, with the fast phase occurring in a random fashion, thus causing marked beat-to-beat variations in the amplitude. In addition, Cogan (1964) pointed out that patients who have a disturbed fast phase, exhibit gaze deviation in the direction of the slow phase and the resulting nystagmus will be scarce and irregular with respect to frequency and amplitude.

Fluur & Mendel (1963) suggested that dysrhythmia is a normal phenomenon linked to adaptive vestibular responses, since they observed that dysrhythmia appeared when normal subjects became habituated during a rotatory test. In an extended study, Fluor (1982) proposed that the dysrhythmia of nystagmus induced by angular acceleration may derive from defence mechanisms activated to avoid overstimulation of the labyrinths.

1.5. Neurophysiological aspects of voluntary eye movements

1.5.1. Initiation of voluntary eye movements

It is generally accepted that voluntary eye movements are initiated by cortical neurons, but the mechanism is obscure (Hoyt & Frisén, 1975). Current hypothesis suggests that the neurons of the frontal eye field (FEF) (Brodmann's area 8) control saccades, while those of the occipital cortex (Brodmann's area 17, 18, 19) are particularly important for smooth pursuit (Hoyt & Daroff, 1971; Gay et al., 1974; Goldberg & Bushnell, 1981).

Nevertheless, the concept of cortical initiation of saccades was challenged by single-unit recordings conducted in untrained monkeys (Bizzi & Schiller, 1970; Mohler et al., 1973; Goldberg & Robinson, 1977), which failed to reveal any presaccadic activity in the neurons of the FEF. However, Goldberg & Bushnell (1981) have shown recently that in trained monkeys a subpopulation of the neurons in the FEF responded selectively to visually guided saccades and were activated to visual intention in advance of the saccades. Furthermore, cerebral blood flow studies in man have indicated a close relationship between voluntary saccades and the FEF (Melamed & Larsen, 1979). The projection of horizontal saccades terminates contralateral to the FEF in the brain stem (Robinson & Fuchs, 1969; Astruc, 1971; Latt & Cowey, 1971; Brodal, 1978).

Clinical observations indicate that unilateral lesioning of the occipital cortex causes deviations in smooth pursuit toward the site of the lesion (Hoyt & Daroff 1971; Sharpe et al., 1979). Furthermore, after ablation of the occipital cortex, degeneration has been noted in the ipsilateral brain-stem nuclei only (Brodal, 1978). The projection of the horizontal smooth pursuit pathway is therefore assumed to cross the midline twice and terminate ipsilaterally in the brain stem (Hoyt & Daroff, 1971).

1.5.2. Parameters of saccades

The relationship between peak velocity and amplitude is the most thoroughly studied of the saccadic parameters (Boghen et al., 1974; Baloh & Honrubia, 1976; Henriksson et al., 1980; Bahill et al., 1981; Pyykkö et al., 1981). A highly synchronous and well-timed barrage of action potentials is needed to trigger a correct saccadic velocity for the amplitude (Robinson, 1975; Gisbergen et al., 1981). Firing of agonistic neurons is accompanied by simultaneous inhibition of antagonistic neurons (Keller, 1974; Hikosaka et al., 1977; Shimazu, 1979). The velocity adaptation is as far as we know integrated by neurons in the PRF. Consistently, in patients with a brain-stem lesion, saccadic peak velocity is reduced, whereas in patients with cerebellar and supratentorial lesions, the peak velocity is generally normal (Baloh et al., 1977; Pyykkö et al., 1981; Wennmo et al., 1983).

Saccadic accuracy is defined as the amplitude of the initial saccade in relation to the desired amplitude (Baloh & Honrubia, 1976). Dysmetria is present in patients with a variety of lesions of the CNS. Hypometria is common in disorders of the frontal lobe and cerebellum (Baloh et al., 1977; Henriksson et al., 1981), basal ganglia (De Jong & Melvill Jones, 1971), superior colliculi (Heywood & Ratcliff, 1975) and brain stem (Henriksson et al., 1981). Hypermetria occurs in cerebellar atrophy, especially during eccentric gaze in a head-fixed position (Jung & Kornhuber, 1964). However, if normal eye-head coordination is not disturbed, hypometria is more common in these cases (Zee, 1977).

Prolonged saccadic reaction time has been reported in patients with lesions of the frontal lobe (Baloh et al., 1977) and a further prolonging of the reaction time in the same patient reflects the clinical progress of degenerative process, e.g. in Alzheimer's disease (Pirozzolo & Hansch, 1981).

Few investigations have been made into the mechanisms responsible for the rhythmic regulation of gaze shifts between two targets. This phenomenon, which may be comparable to diadochokinesis of the hands, requires timing and motor programming. The clinical observations of Holmes (1938), Cogan (1964) and Blackwood et al. (1975) indicate that the integrity of the parietal and frontal cortex is important for correct execution of these types of eye movement.

1.5.3. Parameters of smooth pursuit

Tracking eye movements can be quantitatively analysed by determining the smooth pursuit gain, number and frequency of superimposed saccades, and amplitude of smooth pursuit (Schalén, 1980; Schalén, 1981; Schalén et al., 1982 a).

The analysis of tracking eye movements in patients with various brain lesions provides some idea about the functional organization of the oculomotor system. The system seems highly susceptible to disturbances within brain stem or cerebellum (Raphan & Cohen, 1978; Henn et al., 1980). A preserved function of the brain stem in cases of cerebellar disorder allows some compensation for the defective smooth pursuit by increasing the saccadic component of tracking, whereas in brain-stem lesions this ability to compensate is very limited (Schalén et al., 1982 a). Supratentorial disorders - and especially frontal lobe disorders - cause less prominent disturbances of eye tracking (Schalén et al., 1982 a), supporting the idea that this part of the brain does not participate to the same extent in motor execution of tracking eye movement (Bizzi & Schiller, 1970; Hoyt & Frisén, 1975). In peripheral vestibular disorders only a slight and temporary decrease in smooth pursuit gain is seen, which is well compensated by the saccadic system (Schalén et al., 1982 a,b).

1.6. Purpose of the study

Qualitatively, differences in the nystagmus pattern have been observed to occur in the rotatory test between normal subjects and various groups of patients. Nevertheless, the relevance of nystagmic dysrhythmia has been a matter of controversy. In only a few studies have efforts been made to quantify the variations in intra- or interindividual responses, either in time, amplitude, or velocity frames. Moreover, few clinical reports have concentrated on supratentorial influence on the vestibular nystagmus and the voluntary eye movements.

The objectives of the various works in the present thesis have been:

- (1) to study the applicability of an exponential model for nystagmus during postrotatory response in normal subjects, and to investigate the extent of variation of normal nystagmus, (I);
- (2) to apply the exponential model of postrotatory nystagmus in three groups of patients with different types of vestibular disorder in order to evaluate whether the model is capable of discriminating pathological variations in nystagmus, (II);
- (3) to study intrabeat relationships of postrotatory nystagmus in normal subjects in order to evaluate the extent of normal variation between different nystagmus qualities, (III);
- (4) to apply the intrabeat nystagmus analysis to three groups of patients in order to evaluate the relationship between the site of the lesion and abnormal patterns in intra-beat relationship, (IV);
- (5) to study reflexive and voluntary eye movements in a group of patients with frontal lobe disorder to evaluate the role of the frontal lobe in organizing nystagmus and initiating voluntary eye movements, (V, VI).

2. Subjects and Methods

2.1. Subjects

2.1.1. Normal subjects (I, III)

Normative values and the interindividual variability of nystagmus were studied in 10 normal subjects with a mean age of 41.4 years (range 21-62 years). All subjects were healthy, with normal neuro-otological findings in routine examinations. In 5 of these subjects the test was repeated five times to study the intra-individual variability.

Reaction time of saccades and ability to execute alternately shifting saccades were measured in 20 normal subjects (mean age 48.0 years, range 23-72). The normative values of velocity and accuracy of saccades and velocity of smooth pursuit recorded at this laboratory (Henriksson et al., 1980; Schalén, 1980) were used as reference.

Table I. *Diagnosis, age, duration of symptoms and neurological findings in the patients with peripheral vestibular lesions*

No.	Diagnosis	Age	Duration of symptoms	Neurological findings/signs (L=left, R=right)
1	Vestib.neuropathy	57	2 days	Spont.nyst.L, calor.hyporefl.R
2	Vestib.neuropathy	35	1 week	Spont.nyst.L, calor.hyporefl.R
3	Vestib.neuropathy	39	3 weeks	Calor.areflexia L
4	Vestib.neuropathy	69	2 weeks	Spont.nyst.L, calor.hyporefl.R
5	Vestib.neuropathy	66	5 days	Spont.nyst.L, calor.hyporefl.R
6	Vestib.neuropathy	52	2 weeks	Calor.areflexia R
7	Vestib.neuropathy	61	1,5 months	Spont.nyst.L, calor.hyporefl.R
8	Vestib.neuropathy	61	4 days	Spont.nyst.L, calor.hyporefl.R
9	Labyrinthitis	36	1 day	Spont.nyst.L
10	Mb Meniere	53	4,5 years	Calor.hyporefl.R

2.1.2. Patients (II, IV, V, VI)

Three groups of patients were examined, each consisting of 10 subjects.

- (1) Patients with a peripheral vestibular lesion: 8 suffering from unilateral vestibular neuropathy, with reduced caloric response, one with vestibular dysfunction due to acute middle ear infection and one with Ménière's disease. Ages, diagnoses and duration of symptoms are set out in Table I.
- (2) Patients with a brain-stem disorder: 8 with a brain-stem infarction, one with a vascular malformation in the pons and one with a pontine glioma. Diagnoses, ages, duration of symptoms and neurological findings are given in Table II.

Table II. *Diagnosis, age, duration of symptoms and neurological findings in the patients with brain-stem lesions*

No.	Diagnosis	Age	Duration of symptoms	Neurological findings/ /signs
1	Brain-stem infarction	73	1 month	Left-sided facial nerve palsy, dysphagia
2	Brain-stem infarction	66	2 weeks	Right-sided recurrent nerve palsy, dysphagia
3	Brain-stem infarction	45	2 weeks	Reduced sensibility right side of the face, extensor plantar response left
4	Brain-stem infarction	71	2 weeks	Diplopia
5	Brain-stem infarction	58	2 weeks	Reduced facial and corneal sensibility right
6	Brain-stem infarction	76	1 year	Headache, unsteadiness
7	Brain-stem infarction	71	8 months	Paresis of the right arm
8	Brain-stem infarction	58	6 weeks	Left-sided dysmetria and paresis of the left arm
9	Vascular malformation	73	1 week	Decreased vibration detection threshold in the right leg
10	Pontine glioma	45	1 year	Dysarthria

- (3) Patients with a frontal lobe lesion: 6 had suffered a vascular stroke in the region of the left frontal lobe, 3 had cerebral atrophy of Alzheimer type and one patient had a contusion of the frontal lobe sustained in a traffic accident. Diagnoses, ages, duration of symptoms and neurological findings are given in Table III.

Table III. *Diagnosis, age, duration of symptoms and neurological findings in the patients with frontal lobe lesions*

No.	Diagnosis	Age	Duration of symptoms	Neurological findings/ /signs
1	Infarction	48	11 months	Hemiparesis right
2	Infarction	67	3 weeks	Hemiparesis right
3	Infarction	65	2 weeks	Hemiparesis right
4	Infarction	36	2 years	Hemiparesis right
5	Infarction	73	4 months	Hemiparesis right
6	Infarction	59	2 weeks	Symmetrical reflex enhancements
7	Contusion	25	2 months	Hemiparesis right
8	Atrophy	55	6 months	Right-sided reflex enhancement
9	Atrophy	68	5 years	Symmetrical reflex enhancements
10	Atrophy	67	3 years	Symmetrical reflex enhancements

2.2. Methods

2.2.1. Recording of eye movements (I-VI)

Eye movements were recorded with direct current electro-oculography (EOG) technique using an ink-jet writer (Mingograph M81, Siemens Elema, Stockholm, Sweden) and an analogue filter with an upper cut-off frequency of 15 Hz (Henriksson et al., 1980; Schalén, 1980). Commercial silver-silver chloride electrodes and jelly were used (Medicotest®). The horizontal eye movements were recorded binocularly and the vertical ones monocularly.

2.2.2. Test procedure (I-VI)

The subject was seated comfortably in a chair with the head supported in such a position that the eye-ear axis was horizontal. During the tests, verbal contact was maintained with the subject. In addition to EOG, the eye movements were monitored with an infrared TV camera. The subject was instructed before the test to avoid blinking and to perform the desired eye movements as accurately as possible.

2.2.3. Testing of saccades (V, VI)

The visual targets were variously coloured light diodes mounted on a horizontal bar, placed 120 cm in front of the subject. The pairs of diodes could be switched on-off so that gaze shifts of 5, 10, 20, 30, 40 and 60° would result. The subjects were asked to shift their gaze as quickly as possible between each pair of lighted diodes. Peak velocity of the saccades was measured by manual scoring. The saccades were classified into six categories, with mean amplitudes of 5, 10, 20, 30, 40 and 60° (Henriksson et al., 1980).

Reaction time of saccades was measured for saccades to randomly lighted targets subtending 60° of visual angle. Saccadic accuracy was measured as an amplitude of the initial saccade. At least 10 consecutive saccades at each amplitude and direction were measured.

Ability to execute rapid refixational saccades between alternately shifting targets was measured at light-emitting diode targets placed at visual angles of 20 and 60°. The target shifted between the two positions at time events of 1.2, 1.0, 0.8, 0.6, and 0.4 sec intervals. For a normal response, five correctly spaced saccades at each amplitude and time interval were required.

2.2.4. Testing of tracking eye movements (V, VI)

The target for eliciting tracking eye movements was a light spot, 3 cm in diameter, projected onto a screen placed 160 cm in front of the subject, and moving at various constant velocities of 10, 20, 30, 40, 50 or 60°/sec. The excursion of the target on the screen spanned an amplitude of 60°.

Maximum velocity of smooth pursuit was measured on the part of the recording where smooth pursuit showed its highest velocity, lasting at least 250 msec and starting after an initial velocity adaptation period of 500 msec (Schalén, 1980). The maximum velocity gain of smooth pursuit was calculated as the ratio maximum eye velocity/target velocity.

2.2.5. Testing of angular acceleration induced nystagmus (I-VI)

A rotatory test was conducted in a chair accelerated angularly at 120°/sec for 1 sec in the horizontal plane. After 60 sec the chair was brought to a standstill by a corresponding deceleration. This test was also carried out in the dark with the eyes open.

Velocity, amplitude and duration values of the slow and fast phases of nystagmus were obtained from the recording by manual scoring. The data were fed into a computer and a linear regression analysis was performed on semilogarithmic, logarithmic and non-logarithmic scales. For each postrotatory response, four variables of nystagmus, viz. velocity of slow phase,

duration of slow phase, velocity of fast phase and duration of fast phase, were correlated either to the time course of the response, or in intrabeat analysis to the nystagmus component selected. In the linear regression analysis, intercept (intersection of regression line with y-axis), regression coefficient (slope of regression line) and standard error of regression were determined.

The missing periods of nystagmus were estimated by interpolating the surface area of the nystagmus-free period from the exponential decay of slow phase velocity. The missing amplitudes were accumulated and the results expressed as a percentage of estimated total amplitude.

2.3. Statistics (I-VI)

The statistical significance of the correlation coefficients was evaluated with t-distribution. In the case of dependence of intercorrelations between the variables, the partial correlation coefficients were determined (Edwards, 1979). In repeated tests, the difference between subjects was tested either with Friedman's analysis of variance (Siegel, 1956) or with two-way analysis of variance with repeated test design. The difference between correlation coefficients obtained in linear regression analysis on non-logarithmic vs. logarithmic scales was tested with the Kruskal-Wallis test (Siegel, 1956).

The Mann-Whitney U-test was used to study the difference in the accuracy and reaction time of saccades. The left-right difference of these variables was tested with Wilcoxon's rank sum test. The statistical evaluation between peak velocity of saccades and smooth pursuit curves was made with a two-way analysis of variance with repeated test design. The results in the saccade test on time command were evaluated by using logistic models (Chatterjee & Price, 1977) and the differences in the coefficients in the logistic models were tested with t-distribution. The difference was considered statistically significant when $p < 0.05$.

3. Results

3.1. Studies on applicability of exponential model to postrotatory nystagmus variables (I, II)

3.1.1. Normal subjects (I)

The various nystagmus variables analysed are schematically presented in Fig. 1.

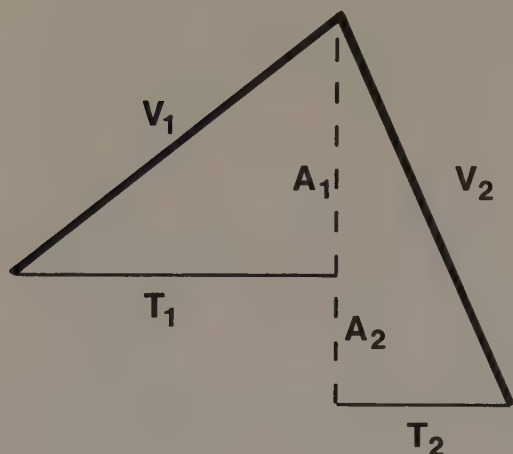


Fig. 1. Variables of nystagmus beat. Abbreviations: A_1 slow phase amplitude, A_2 fast phase amplitude, T_1 slow phase duration, T_2 fast phase duration, V_1 slow phase velocity, V_2 fast phase velocity.

Linear regression analysis was fitted to slow-phase velocity (V_1) and duration (T_1) as well as to fast-phase velocity (V_2) and duration (T_2) on semilogarithmic scales. In individual response patterns the regression coefficients of V_1 and T_1 showed highly significant differences. No such differences were found in V_2 and T_2 .

For the intercept of the responses a statistically significant difference was found between the subjects regarding all nystagmus variables (for V_1 , T_1 and T_2 , $p < 0.001$, for V_2 , $p < 0.01$).

Standard error of regression for each nystagmus variable in the group was 0.175 for V_1 , 0.356 for T_1 , 0.264 for V_2 and 0.340 for T_2 . Significant differences between the individuals were found with respect to V_1 ($p < 0.01$) and T_1 ($p < 0.05$).

Consequently, the response course - and hence time constant of postrotatory nystagmus - was coupled to individual factors in variables V_1 and T_1 only. In the adaptation of the regression line to the observations as expressed in standard error of regression, variables V_1 and T_1 exhibited significant inter-individual differences. In the response, maximum significant interindividual differences occurred for all nystagmus qualities. These findings may be regarded as "normal dysrhythmia" in the exponential model.

3.1.2. Patients with neurological disorders (II)

In the exponential model the regression line describing V_1 declined more steeply in patients with a brain-stem lesion, yielding significantly lower values for the regression coefficient ($p < 0.05$), than in other groups of patients or in normal subjects (Table IV). On the intercept of V_1 , patients with a frontal lobe lesion scored higher values than any other group of patients. The difference in intercept was statistically significant ($p < 0.05$). As regards regression coefficient and intercept of T_1 , V_2 and T_2 , no statistically significant differences were discerned between the patients and normal subjects.

The standard error of regression was of about the same magnitude in normal subjects as in patients with different types of disorder. No statistically significant inter-group differences could be distinguished for this parameter.

Table IV. *Time constants of V_1 for normal subjects and the different groups of patients, obtained from linear regression analysis (time constant = $1/\text{regression coefficient}$)*

Subject no.	Normal (sec)	Vestib. periph. (sec)	Brain stem (sec)	Frontal lobe (sec)
1	11.8	10.2	10	7
2	17.7	5.6	9.9	10.3
3	15.2	3.2	5.2	24.4
4	15.5	12.7	6.2	15.3
5	21.1	9.4	8.5	12.8
6	23.4	28.6	11.4	15.3
7	11.1	9.8	11.8	16.3
8	19.3	15.4	10.6	3.7
9	25.0	10.9	14.4	10.1
10	5.4	12.7	9.9	13.2

The pauses occurring during nystagmus were analysed quantitatively as missing amplitude of the total slow phase deviation and expressed in percentage. Patients with a frontal lobe lesion differed from other groups of patients and from normal subjects by having more pauses during the nystagmic response. The difference was statistically significant ($p < 0.01$) (Fig. 2).

Thus, pathological dysrhythmia may be traced in the exponential model as hyperresponsiveness of V_1 or as frequent pauses in nystagmus, as evidenced by the patients with a frontal lobe lesion. Pathological dysrhythmia may also appear as nystagmic fatigue, as in the patients with a brain-stem lesion. It is noteworthy that pathological dysrhythmia did not appear with an increased spread of nystagmus beats around the regression line.

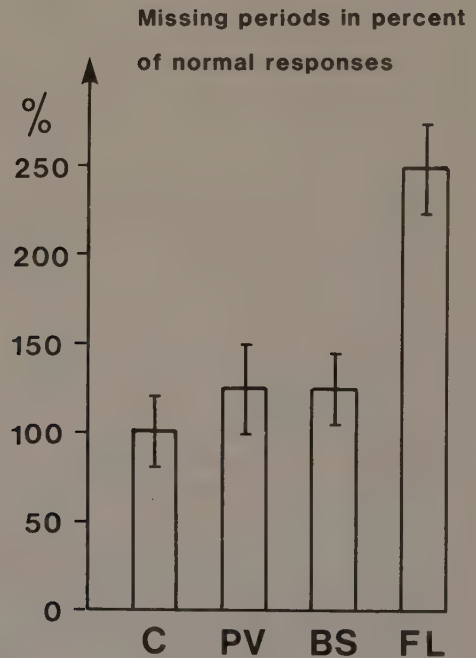


Fig. 2. The magnitude of nystagmus-free intervals during postrotatory responses in normal subjects and in the different groups of patients. Values are expressed as percentages of normal values. Mean and standard deviation are given.

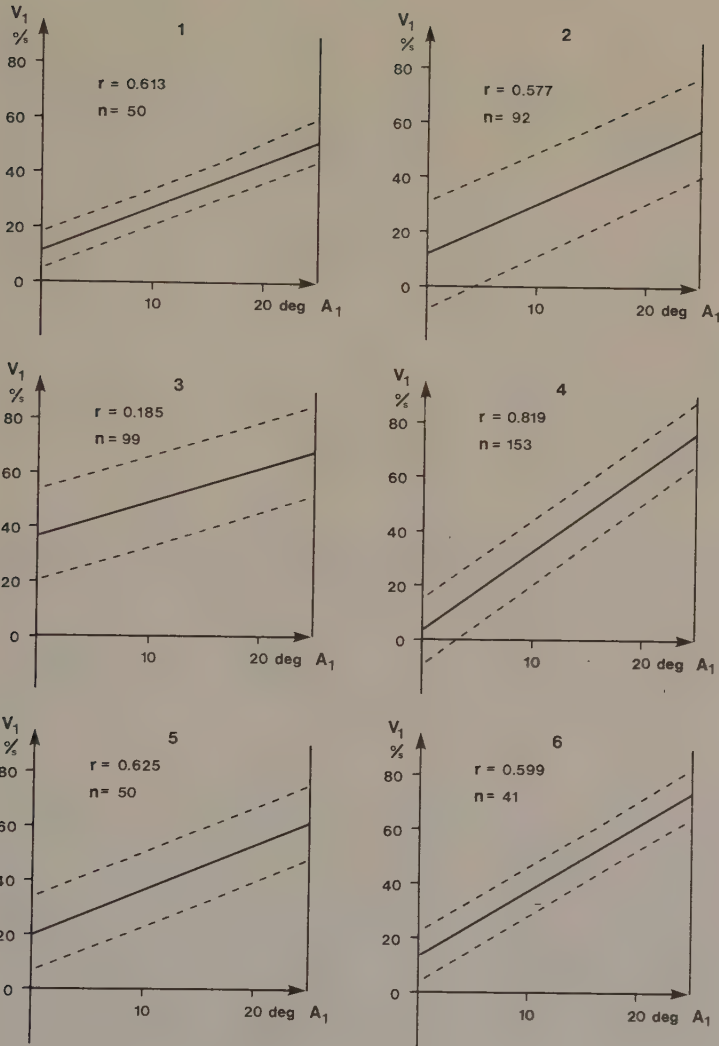


Fig. 3. Relationship between V_1 and A_1 in linear regression analysis in 6 normal subjects. Regression line, standard error of regression, correlation coefficient and number of observations are set out. The order of each test subject is shown in the figure.

3.2. Intrabeat relationship of postrotatory nystagmus (III, IV)

3.2.1. Normal subjects (III)

A close correlation was found between velocity (V_1) and amplitude (A_1) of the slow phase nystagmus in normal subjects ($r(861) = 0.523$, $p < 0.001$). In individual responses a statistically significant correlation between V_1 and A_1 was established in all subjects (Fig. 3). When repeating the test five times in 5 of the subjects, they generally responded in the same manner at each test ($p < 0.05$). Fig. 4 shows the relationship between V_1 and A_1 on repeated testing in one of the subjects.

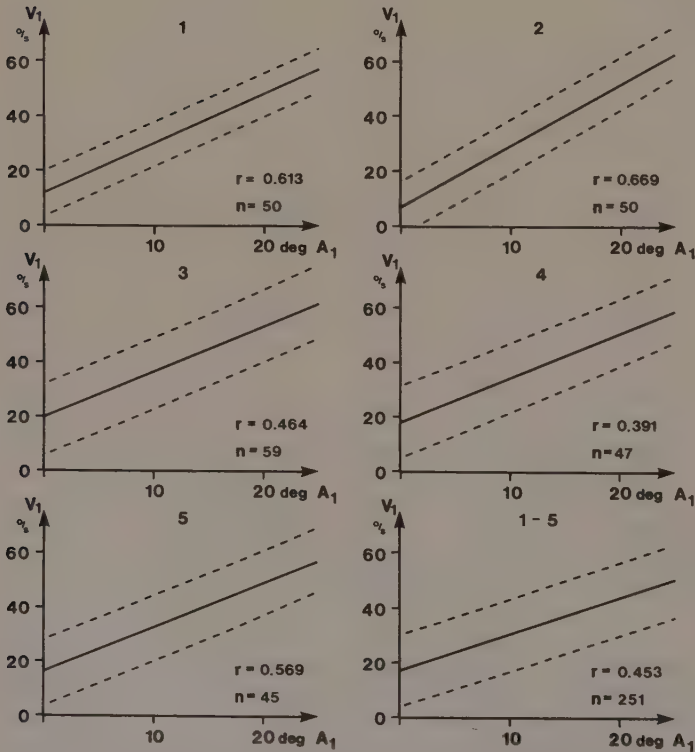


Fig. 4. Relationship between V_1 and A_1 in linear regression analysis at repeated testing in subject No. 1. Regression line, standard error of regression, correlation coefficient and number of observations are given.

The linear regression analysis between V_1 and T_1 showed a statistically highly significant correlation ($r(861) = -0.470$, $p < 0.001$). In individual testing, all the subjects showed a significant relationship between V_1 and T_1 . In repeated tests conducted in 5 of the subjects, a consistent response pattern was generally observed ($p < 0.05$) in regard to these variables. Logarithmic conversion of the axis did not significantly improve the correlation.

Partial correlation coefficients calculated for the relationship between T_1 and A_1 showed that they were not mutually correlated, as was expected.

The correlation between amplitude of slow (A_1) and fast phase (A_2) was statistically highly significant ($r(861) = 0.678$, $p < 0.001$). In these nystagmus qualities the individual response pattern was much the same in all subjects and no significant variation could be observed in repeated tests.

Thus, normally both A_1 and T_1 are closely correlated with V_1 and influence the end-point of nystagmus. Presumably the different fast-phase qualities are determined to a considerable extent by A_1 , which is closely correlated with A_2 .

3.2.2. Patients with neurological disorders (IV)

In linear regression analysis between V_1 and A_1 , patients with a brain-stem lesion scored lower values on the intercept than did normal subjects ($p < 0.05$). As regards the regression coefficient and the correlation coefficient, no statistically significant differences were observed between the groups studied. It was noteworthy that patients with different types of lesions showed remarkable interindividual variability in the responses. An example of such variability is set out in Fig. 5, illustrating 6 patients with a peripheral vestibular lesion.

In linear regression analysis between V_1 and T_1 , patients with different types of lesions scored lower correlation coefficients than did normal subjects. The correlation coefficients were -0.402 for patients with a peripheral vestibular lesion, -0.280 for patients with a frontal lobe lesion and -0.237 for patients with a brain-stem lesion, whereas it was -0.470 for normal subjects. Consistently the regression coefficients tended to approach zero in the different groups of patients when compared with the normal subjects. The difference between normal subjects and the patients was statistically significant ($p < 0.01$). Fig. 6 shows individual regression lines for 6 patients with a brain-stem lesion.

In pairwise comparison, differences in the regression coefficient were found between normal subjects and patients with a vestibular peripheral disorder ($p < 0.05$), between normal subjects and patients with a frontal lobe disorder ($p < 0.01$) and

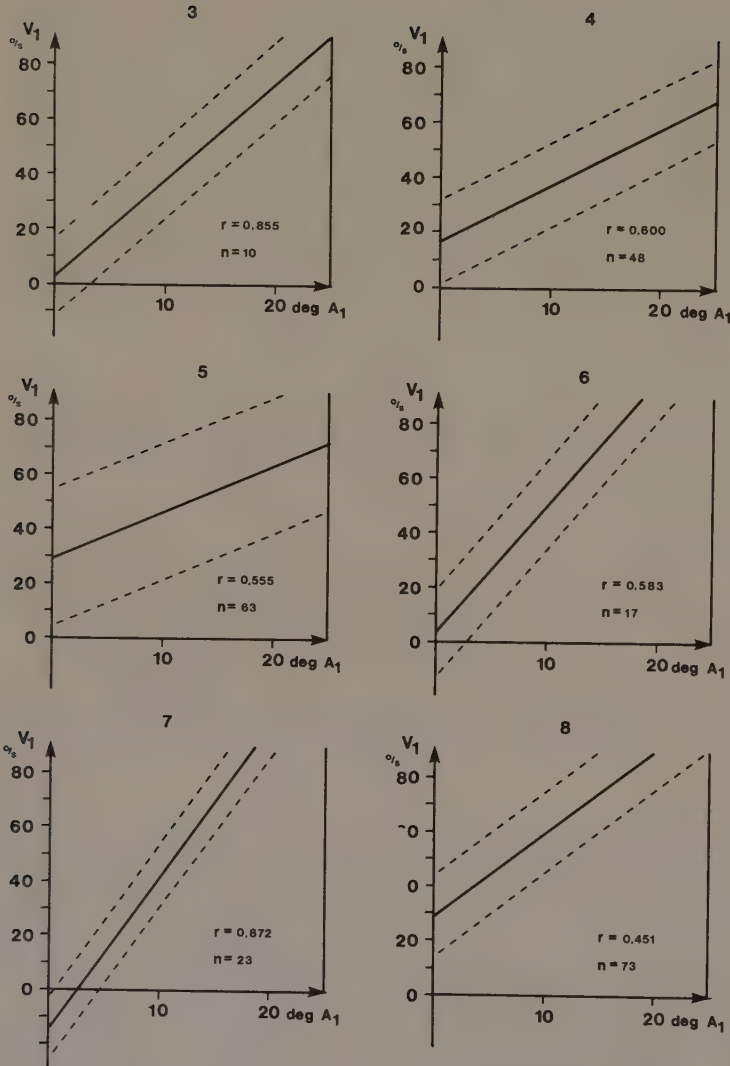


Fig. 5. Relationship between V_1 and A_1 in linear regression analysis in 6 patients with a peripheral vestibular lesion. Regression line, standard error of regression, correlation coefficient and number of observations are given. The order of each subject is shown in the figure.

between normal subjects and patients with a brain-stem disorder ($p < 0.001$). In addition, on the intercept, statistically significant differences were found between normal subjects and patients with a frontal lobe lesion ($p < 0.05$) and between normal subjects and patients with a brain-stem lesion ($p < 0.001$).

In linear regression analysis between A_1 and A_2 , no significant differences were found in intercept, regression coefficient, or correlation coefficient, which would distinguish between the various groups of patients and normal subjects.

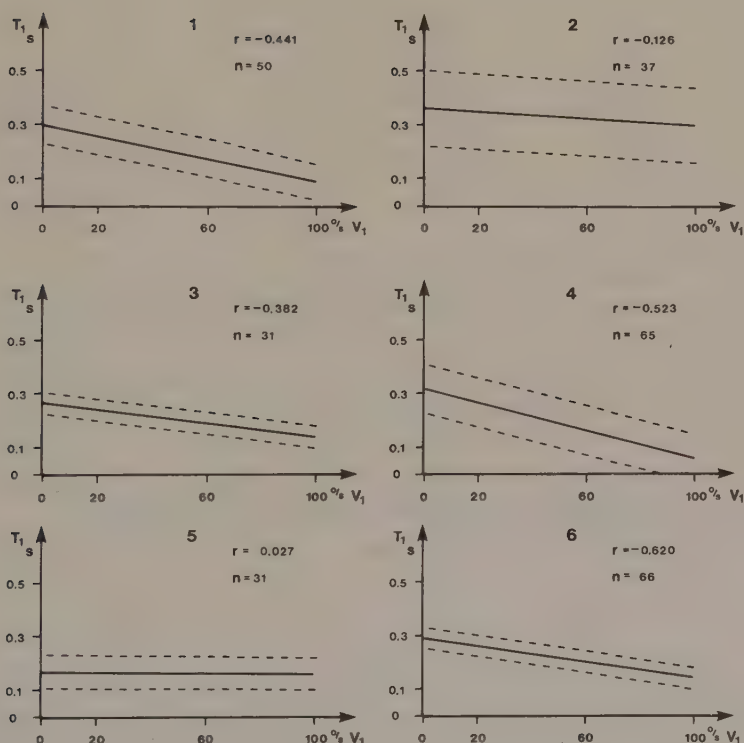


Fig. 6. Relationship between T_1 and V_1 in linear regression analysis in 6 patients with a brain-stem disorder. Regression line, standard error of regression, correlation coefficient and number of observations are given. The order of each subject is shown in the figure.

The results indicate that a lesion at any site in the VOR arch impairs the control of the end-point of the slow phase of nystagmus exerted by amplitude. Correspondingly, other mechanisms are employed to a greater extent in the control of the end-point of nystagmus. Thus, in intrabeat analysis, nystagmic dysrhythmia may appear as a disturbed relationship between nystagmus qualities of V_1 and T_1 as well as of V_1 and A_1 .

3.3. Oculomotor control in patients with lesions in the frontal lobe (V , VI)

Considered qualitatively, optokinetic and vestibular responses were normal in the patients with a frontal lobe lesion, whereas voluntary saccades and smooth pursuit were disturbed. The most profound differences observed between normal subjects and the patients were the far less accurate saccades in the patients.

In the quantitative analysis of the eye movements the saccadic inaccuracy occurred in both directions ($p < 0.001$) (Fig. 7). The latency period in normal subjects was on average 270 msec, whereas in the patients it was prolonged - on average 320 msec to the left ($p < 0.01$) and 420 msec to the right ($p < 0.01$). The difference in latency between left and right saccades was also statistically significant ($p < 0.01$). The peak velocity of the saccades was normal in saccades to the right but reduced to the left ($p < 0.01$). Ability to produce saccades on time command was poor in the patients, when compared with normal subjects ($p < 0.001$).

Maximum velocity gain of smooth pursuit was reduced when compared with normal subjects. Maximum velocity gain was reduced rather more in smooth pursuit to the right ($p < 0.001$) than to the left ($p < 0.01$).

The maximum velocity of postrotatory nystagmus tended to be increased in patients when compared with normal subjects, but the difference was not statistically significant.

Thus, patients with frontal lobe lesions had evident difficulty in executing voluntary eye movements, whereas nystagmus responses tended to be hyperactive.

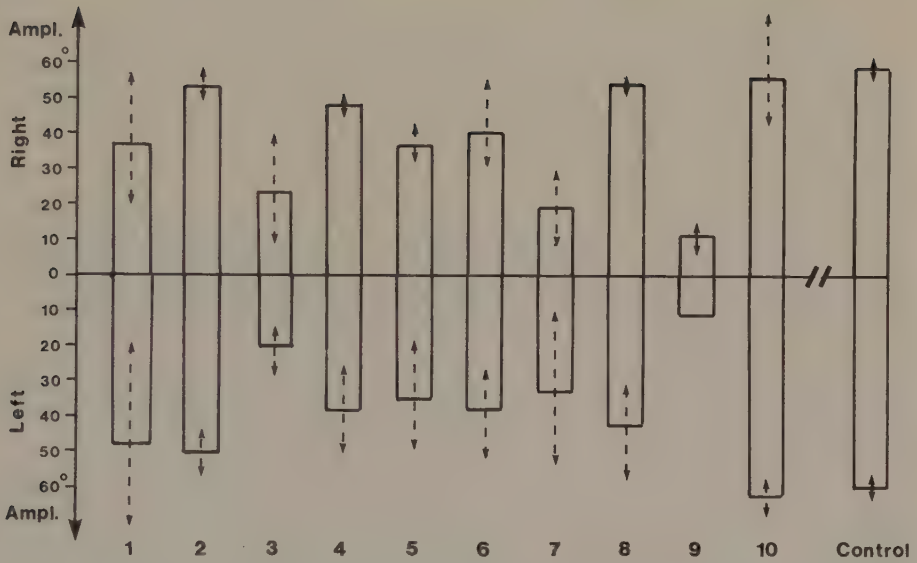


Fig. 7. Saccadic accuracy in 10 patients with a brain-stem lesion and in 20 control subjects. Saccades to right and left are shown upwards and downwards, respectively. The order of each patient is shown in the figure. Mean and standard deviation are given.

4. Discussion

4.1. General findings

(I, II). By applying an exponential model, interindividual differences were found among normal subjects in the maximum velocity of V_1 , time constant of V_1 and in standard error of regression of V_1 and T_1 . In the fast phase of nystagmus, in general, a shortage of statistically significant interindividual differences was met with.

In the patients the maximum velocity of V_1 was significantly increased in the cases with a frontal lobe lesion, whereas the time constant of V_1 was significantly shortened in the cases with a brain-stem lesion. Moreover, patients with a frontal lobe lesion exhibited pauses in nystagmus more frequently than did other groups.

(III, IV). The analysis of intrabeat relationship suggests that the end-point of V_1 is determined by two control circuits, one keeping a record of A_1 and one of T_1 . Presumably at high nystagmus velocities the durational circuitry predominates over positional circuitry in order to allow sufficient time for fixation. In patients with various disorders, the function of durational circuitry was better preserved than that of positional circuitry. Consistently the dependency of the end-point of V_1 on A_1 became less dominant.

(V, VI). In patients with frontal lobe lesion the voluntary eye movements were far worse, whereas the reflexive eye movements were normal or even facilitated. In particular, initiation of the saccades and control over their excursion were both disturbed. Smooth pursuit was reduced in maximum velocity gain. The findings indicate that the frontal lobe pre-programs and controls eye movements.

4.2. Comments on the methods

4.2.1. Rotatory test (I, II)

In the present test, the interval between successive rotatory tests to left and right was for practical reasons short, viz. 60 sec. The secondary phase of nystagmus which usually appears 30 to 40 sec after accelerating or decelerating the chair, may thus influence the postrotatory responses (Aschan, 1967) or cause frequent pauses in the nystagmus (Fluur, 1982). Nevertheless, since the same test schedule was employed in the control subjects as in the patients, the differences observed in the results cannot be attributed to this factor. However,

the magnitude of pauses in the nystagmus or the degree of velocity variation may diminish if longer time intervals are used, e.g. 5 min, as proposed by Aschan (1967). When comparing the present results with other studies, this difference in the methods should be kept in mind.

Since the classical acceleration-deceleration test was introduced by Bárány, other types of rotatory stimuli have been applied in research and in clinical work, for instance a pseudo-random acceleration test with a frequency range of 0.01-0.3 Hz (O'Leary et al., 1976; Wall et al., 1978), slow harmonic acceleration at frequencies of 0.01-0.16 Hz (Wolfe et al., 1978), rapid harmonic acceleration at frequencies of 0-6 Hz (Schwarz & Tomlinson, 1979; Hydén et al., 1982), and random sinusoidal acceleration at frequencies of 0-6 Hz (Hydén et al., 1983). Compared with the rotatory test a.m. Bárány, these new stimuli offer one advantage, namely they cover a large frequency range of vestibular responses and consequently enhance the accuracy of the test results. However, there is still no convincing evidence that non-conventional rotatory stimulation is superior to the Bárány test - at least in clinical work. Since the nature of the stimulus differs between different tests, the present results are not directly applicable to them. Especially in the newer tests with continuously changing acceleration, the relatively long time constant of nystagmus in man (15 sec) may alter the nystagmic pattern in detailed analysis.

4.2.2. Statistical work-up (I-IV)

In linear regression analysis the correlation coefficient indicates how well the line represents the distribution of the points. Thus, for example, in the relationship between A_1 and A_2 the correlation coefficient yielded 0.678. This value, even though statistically highly significant, explained only 46% of the variation between observations; the rest was attributable to other factors, e.g. independence and measuring errors. Thus, even though the variables are strongly correlated, the bulk of the observations may not reflect this relationship, indicating that other relationships, not illustrated in the present study, may still exist.

It is noteworthy that if the correlation coefficient scores a low value, the rest of the parameters in the linear regression analysis will suffer from vagueness. Furthermore, it must be stressed that the intercept in the regression analysis is not identical with the maximum value of postrotatory response, but is an estimate thereof. Especially if the values are logarithmic, the confidence limits of the intercept will become extended. Since neither parametric nor non-parametric statistics, as used in the present work, take into consideration this vagueness, the significance of the statistical statements regarding this parameter should be viewed in a more or less descriptive fashion.

4.2.3. Selection of the patients (II, IV-VI)

As previously stressed by several researchers (e.g. Riesco-MacClure, 1964; Schalén, 1981), electro-oculographical studies in patients may have certain drawbacks, as pathological lesions in man cannot be compared with strictly defined experimental lesions in animals. Furthermore, due to plasticity of the CNS the disturbance may exhibit different clinical expressions, e.g. depending on the extent and the site of the lesion, its pathology, time course, age of the subject, etc. The interpretation may also be blurred by clinically silent lesions. Consequently, in man we can never be completely confident with topographical diagnosis of the lesion and the site of the specific functional disturbance.

However, since the eye motor system in man works with great prediction and depends on volition (Fleming et al., 1969; Hörnsten, 1979; Findlay, 1981), it is conceivable that the oculomotor test in man may give different results than in monkey (cf. Hoyt & Frisén, 1975; Goldberg & Bushnell, 1981). Furthermore, in the clinical work-up of oculomotor disorders the complexity of pathological lesions more closely resembles for natural reasons lesions in patients than do experimental lesions in animals. Therefore studies on humans, as in the present work, will still be necessary.

4.3. What is dysrhythmia of nystagmus? (I-IV)

Allegedly, the majority of dysrhythmias may be theoretically regarded as stemming from variations in the time and amplitude frame of nystagmus. These variations will cover changes within one beat and between successive beats, like variations in amplitude, duration and velocity, or variation in the temporary course of nystagmus. A combined variation of amplitude and time frames of nystagmus will cause the more complicated dysrhythmias, e.g. salvos, different group formation and secondary nystagmus.

In intrabeat analysis of nystagmus, differences in the control mechanisms of nystagmus were actually observed. After a lesion affecting the vestibular system the time control over nystagmus increased and the nystagmus response became automatized regarding the amplitude resetting mechanisms. In the patients with a brain-stem lesion the time frame of the nystagmus became fixed and the resulting postrotatory nystagmus had characteristics of petit ecriture type of nystagmus. Thus, automatization of an amplitude resetting mechanism may be regarded also as pathological dysrhythmia of nystagmus.

Nevertheless, deviation in the velocity of slow and fast phase can also give rise to dysrhythmia of nystagmus. The observations made by Fluor (1982) suggest that irregularities in the nystagmus response might also depend on the inhibition of the velocity information to the central or peripheral vestibular system. Thus, pauses would depend on a complete inhibition

of the velocity information derived from the vestibular end organs.

Short periods of nystagmus suppression have been considered to be a normal defence against excessive stimulation (Fluur, 1982). In the present study, nystagmus-free periods were found among normal subjects remarkably often, thus supporting this idea. However, the magnitude of the pauses was excessive in patients with a frontal lobe lesion. The faulty nystagmus response among these patients may be due to dysfunction of the FEF and hence indicate an impaired control of FEF over nystagmus. Since pauses in nystagmus also occurred frequently among control subjects, caution should be taken in interpreting a nystagmus response as pathologic on the basis of nystagmus-free periods only.

4.4. Comments on suitability of exponential model for dysrhythmia evaluation (I, II)

In the present results the dysrhythmia was approached by fitting different components of nystagmus in an exponential model. Theoretically, deviations from the model might appear in the form of changes in the intercept, regression coefficient, or standard error of regression. In the normal subjects, such deviations were observed mainly in the intercept and the regression coefficient of V_1 , but to some extent also in T_1 . Nevertheless, in the standard error of regression, describing the average distance which the observed values are scattered around the regression line, differences in V_1 and T_1 were observed between the normal subjects only.

Only two parameters among those studied, namely the intercept of V_1 and regression coefficient of V_1 , differed significantly between normal subjects and patients. These findings support the concept of the basic need for great stability of the VOR arch.

Nevertheless, since the fast phase of nystagmus is not derived from the end organ, but processed in the central vestibular system, the exponential model is insufficient to reveal abnormality in the fast phase. As indicated in other reports, the relationship between the amplitude and the peak velocity of the fast phase seems to be a good indicator of abnormalities in the fast phase (Henriksson et al., 1980; Pyykkö et al., 1981).

4.5. Comments on intrabeat relationship of nystagmus (III, IV)

The vestibular system can be regarded in simplified form as a high-pass filter which perceives head velocity and causes a compensatory eye deviation in order to allow unblurred fixation. The velocity signal in VOR is processed without feed-back as in an open-loop system (Buizza & Schmid, 1982). Hence the system is sensitive to variations in the environment and corollary circuits are necessary to counteract oversensibility and to control the response. If the vestibular responses are studied

in the dark, as in the present study, the determinant of the positional signal of the eyes must be derived outside the visual resetting system.

Since there is no functional stretch reflex in VOR (Keller & Robinson, 1971), a proprioceptive resetting mechanism is less likely to determine the end-point of the slow phase of nystagmus. In the transfer function of the VOR, velocity signal is employed rather than positional signal (Buizza & Schmid, 1982). This renders the velocity signal likely to determine the end-point of nystagmus (integration of velocity over time produces positioning of the eye). Actually, measurements made during optokinetic nystagmus indicate that when the stimulus is kept constant, the main factor determining the duration and amplitude of nystagmus is eye velocity (Lau et al., 1978). Consistently in the present study the velocity signal was correlated to the amplitude of the slow phase.

The present results also indicate that duration of slow phase of nystagmus is correlated with velocity of the slow phase. Thus, the end-point of nystagmus is, in some circumstances, probably influenced also by the duration of nystagmus beat. This control system seems to operate independently of the amplitude control mechanisms.

Such a model, where corollary discharge is controlling a movement pattern, is known as an efferent copy and has been proposed to operate during optokinetic nystagmus and voluntary eye movements (see Henn et al., 1980). The present results tend to confirm that two corollary circuits - "durational" and "displacement" - are operating during vestibular nystagmus in the dark. Moreover, it seems likely that the "durational" circuit determines the end-point of nystagmus when the eye velocity is high, whereas "displacement" circuit does it when the eye velocity is low. This arrangement seems feasible from the physiological point of view; the visual target has to be kept in retina long enough to allow unblurred fixation.

In lesions affecting the vestibular system, the relationship between A_1 and V_1 showed a tendency to become closer. Such a close linkage indicates increased automation in the amplitude setting mechanisms. Also, differences in the degree of vulnerability of the amplitude control mechanism were observed in the patients. Those with a vestibular peripheral lesion were the least affected and those with a brain-stem disorder, the most affected. It was noteworthy that in the patients with a brain-stem lesion the duration of nystagmus seemed to be time-fixed, the mean duration of nystagmus varying between 0.15 and 0.25 sec. This period applies to the occurrence of fast phases having a frequency of 3 to 4 Hz. According to Donaghy (1980) 4 Hz seems to be the maximum number of fast-phase events still ensuring unblurred fixation during slow phases.

The patients with brain-stem lesions responded with lower nystagmus amplitudes to a given velocity than did normal

subjects. Since the regression coefficient did not differ between these groups, the brain-stem group needed a higher slow-phase velocity to generate the same amplitude of nystagmus as did the normal subjects. This elevated threshold for the release of amplitude seems to be a contributory factor in the origin of the petit ecriture type of nystagmus met with in patients with brain-stem lesions.

4.6. Frontal lobe and eye movements - an unresolved problem? (V, VI)

A movement pattern of the eye requires intact perception, pre-programming of the motor events, execution of the movements and control of their accuracy. The neuronal subpopulation of the frontal eye field (FEF) seems to fulfil all but motor execution of the eye movements. Thus, FEF neurons have quite a large visual field (Mohler et al., 1973; Goldberg & Bushnell, 1981). They exhibited presaccadic activity capable of initiating voluntary eye movements (Goldberg & Bushnell, 1981). FEF neurons also receive information during and after eye (and head) movements, indicating some degree of control function (Bizzi & Schiller, 1970).

Much of the clinical picture in the frontal lobe syndrome is attributed to failure to feed relevant information into the consciousness and to set different motor or sensory tasks in their proper time frames (Luria, 1980). Consequently patients with a frontal lobe lesion characteristically exhibit lack of attention and defective short-term memory (Brody & Pribram, 1978). In extensive lesions the time frame may be completely missing (Luria, 1980). The same types of disturbance as reported in the timing of sensory messages can also be observed in the motor performance of these patients (Geschwind, 1975).

In the programming of the voluntary saccades, determination of the extent of activation of agonistic extra-ocular muscles and inhibition of the antagonistic extra-ocular muscles within the frame of movement of the head are important (Gisbergen et al., 1981). If the time concept becomes faulty, the pacing of individual eye movement sequences will fail, in consequence. Saccades will become inaccurate and some retardation may arise (Starr, 1967). Correspondingly, as shown in the present study, the peak velocity of the saccades tends to be reduced contralateral to the lesion, whereas they are normal ipsilaterally. A similar finding has been observed after hemispherectomy. (Troost et al., 1972). Since the neural population mediating the velocity-amplitude performance of the saccades is located in the brain stem (Raphan & Cohen, 1978) and the FEF is not directly involved in the velocity matching of the saccades (Goldberg & Bushnell, 1981), the reduction in saccadic peak velocity must be due to a defective "command message".

Visual negligence and inattention to contralateral saccades may also interfere with the saccadic command signal given by the FEF (Latto & Cowey, 1971). Since we observed no side

differences in the accuracy of the saccades, this explanation seems less likely.

Striking disturbances in eye motor performance were found in the test where gaze was shifted between targets on time command. All the subjects evidenced difficulties in executing saccades. It is conceivable that the setting of different eye movement events in the correct time frame was impaired in these patients. In this respect the oculomotor behaviour closely resembled the apraxia of their speech.

The smooth pursuit eye movements were reduced in the maximum velocity and the smooth pattern was replaced by superimposed saccades. Since smooth pursuit is executed to a great extent by prediction (Stark et al., 1962), the impaired capacity to follow could be ascribed to the lesion of the neural mechanism's pre-programming of memorized movements (Geschwind, 1975). Since smooth pursuit requires visual attentiveness during its execution, a defect in the attention span met with in disorders of the prefrontal cortex (Fuster, 1980) might explain the impaired smooth pursuit in patients with frontal lobe lesion.

5. Conclusions

In the present study nystagmic deviations occurring in time, amplitude and velocity frame were examined in normal subjects and in three groups of patients. In addition, the supratentorial control mechanisms of nystagmus and voluntary gaze were explored in a group of patients with a frontal lobe lesion.

1. Velocity and duration of the slow phase, but not the velocity and duration of the fast phase of postrotatory nystagmus showed good suitability to an exponential model. The response course, maximum responsiveness and beat to beat variability for slow phase velocity and duration showed significant interindividual variability.
2. In the exponential model the slow phase velocity of the patients with a brain-stem lesion deviated statistically significantly from normal subjects and from patients with vestibular peripheral lesion with respect to time constant. Patients with a frontal lobe lesion responded with a higher response maximum and exhibited more frequent pauses than did normal subjects or other groups of patients. The exponential model showed a shortage of differences in any other nystagmus parameter studied.
3. In intrabeat relationship of nystagmus the slow phase velocity shares a significant correlation with the amplitude and duration of the nystagmus as studied by linear regression analysis. Individual responses were persistent and repeatable. Allegedly, in determining the end-point of nystagmus, amplitude control as a nystagmic resetting mechanism is mainly employed. However, during high slow-phase velocities the nystagmic resetting mechanism will be shifted towards time control to allow a sufficiently long interval for fixation during a slow phase.
4. Irrespective of the site of their lesion, patients exhibited reduced ability to control the end-point of nystagmus by amplitude mode and instead shifted the control of nystagmic resetting mechanisms towards time. Patients with a brain-stem lesion showed almost complete loss of amplitude control and exhibited nystagmus with fixed slow-phase duration which is clinically designated petit ecriture of nystagmus.
5. In patients with speech dyspraxia due to a frontal lobe lesion, analysis of the eye movements showed that saccadic accuracy was reduced, reaction time was retarded and peak velocity was slowed contralateral to lesion. The patients

had profound difficulties in executing saccades in time command. Smooth pursuit was reduced bilaterally. Vestibular responses were hyperactive. Thus, the frontal lobe seems to exercise control over nystagmus and pre-program voluntary eye movements, presumably by setting different movement sequences in their correct time frame.

The present study provides information on the control mechanisms of nystagmus and voluntary eye movements. The results indicate that various deviations occurring in time, amplitude and velocity frame, either in a nystagmus beat or during a nystagmus response, are to a great degree a normal phenomenon. In quantitative analysis, however, differences can be observed between normal subjects and patients with different types of vestibular lesion. Consequently a deeper analysis of nystagmus pattern may provide additional data on the site of lesion.

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THE DYSRHYTHMIA AND THE EXPONENTIAL CONSTANTS OF THE POSTROTATORY NYSTAGMUS QUALITIES

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Abstract. In 5 healthy individuals the postrotatory, exponential constants were estimated for each of the four nystagmus qualities, viz. the velocities and durations of the fast and slow components. The residual spread (S_r) for each quality in a semilogarithmic plot was also determined. The value of the constant for postrotatory decay indicated a decrease of the velocity and an increase for the duration of the slow component, both with a significant difference between individuals, while for the corresponding values of the fast components no systematic change in the postrotatory reactions was indicated, nor any difference between individuals. The constant that corresponds to the value at maximum stimulus showed differences between individuals for each of the four nystagmus qualities, while S_r presented differences between individuals only for the two slow phase qualities. This technique to describe postrotatory nystagmus reactions by the two exponential constants for each of the four nystagmus qualities together with the residual spread for each of the qualities is intended for future 'on-line' nystagmus analysis.

A varying degree of irregular nystagmus pattern (dysrhythmia) is frequently met with in clinic as well as in postrotatory nystagmus reactions. Some authors stress the existence of pauses in which no nystagmus can be seen, while others claim that an irregularity in the nystagmus beats is the most important sign of dysrhythmia (Aschan et al., 1956; Resco-MacClure & Stroud, 1960; Clément, 1970).

In the present study the quantification of dysrhythmia is based upon the assumption that a nystagmus beat is made up by four different qualities, viz. the velocities (V_1 and V_2) and durations (T_1 and T_2) of slow and fast components (Fig. 1). A series of nystagmus beats can then be represented by four different series of values, each series representing one

of these qualities. A dysrhythmia in a series of nystagmus beats could then be defined as the statistical spread within any of these series.

However, a varying vestibular stimulus could contribute to the statistical spread. Therefore, such variation should either be compensated for or otherwise be taken into account (Henriksson et al., 1976) so that only the "extravestibular spread" is measured.

As the rotatory stimulus can be well defined and is easily reproducible (Fluur & Mendel, 1969), we have in the present paper chosen to direct our interest to dysrhythmia of postrotatory nystagmus responses.

INTRODUCTORY DISCUSSION

According to van Egmond et al. (1949) the solution of the equation determining the postrotatory return of a deviated, overdamped cupula/pendulum can be approximately written as

$$\xi = \xi_0 \cdot e^{-a_1 T} \quad (1)$$

In this equation ξ represents the angular deviation of the pendulum (cupula), a_1 the rate of decay of the pendulum (cupula), T the time and ξ_0 the peak value of deviation of the pendulum (cupula).

As the postrotatory velocity of the slow component (V_1) has been found to grossly reflect the deviation of the cupula (ξ) (Dohman, 1925; Hallpike & Hood, 1953; Groen, 1956) we adapt the sequence of V_1 to an ex-

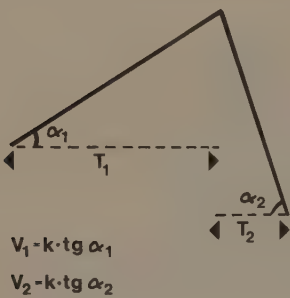


Fig. 1. The four nystagmus qualities.

ponential function similar to (1). For the case that this is done with full success we have

$$\log V_1 = a_1 T + a_2 \quad (2)$$

This means that the log velocity of slow component in a postrotatory nystagmus response plotted against time is a linear function of time (T) in which the rate of decay is expressed by the value of a_1 and the initial value by a_2 . A spread around the line will indicate a 'dysrhythmia' which cannot be related to an exponential decay.

In order to measure the spread and estimate the parameters a_1 and a_2 we have applied linear regression. The residual spread (S_r) (Rao, 1965) around the estimated line is used as a measure of dysrhythmia.

As we cannot exclude that not only V_1 but also the other qualities may vary with vestibular stimulus we have applied the same technique also to V_2 , T_1 and T_2 .

The determination of the S_r value for each of the four nystagmus parameters in rota-

tory nystagmus reactions will provide for each quality an expression for dysrhythmia. This is true even if an exponential decay cannot be found.

The introduction and the determination of this residual spread as an expression for dysrhythmia of each of the four nystagmus qualities in postrotatory nystagmus have been one of the objectives of the work. Since the calculations are based on the two exponential constants that correspond to the decay and the initial value respectively these constants have also been studied.

The specific aim of this work was to employ a computer technique to determine in five normals and in repeated postrotatory nystagmus reactions for each nystagmus quality, the three parameters:

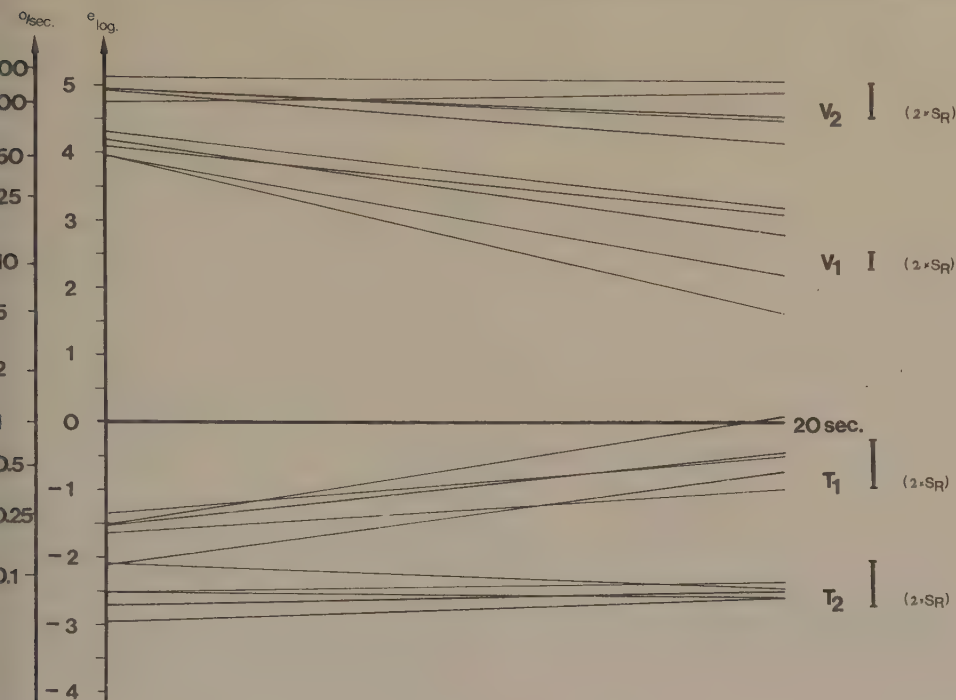
1. the rates of decay (a_1), with particular attention to differences in decay between nystagmus qualities and between individuals;
2. the estimated initial values and their 'logs' (a_2), with the possibility to construct for each individual a normated (i.e. to maximum stimulus) nystagmus beat—again with special attention to differences between individuals;
3. the residual spread (S_r), with particular attention to differences between qualities and to differences between individuals.

METHODS

Clockwise angular stimulations of 120°/sec for 1 sec were used. The rotation lasted for 60 sec and was followed by a deceleration

Table I. Mean (M) and spread (S) in $a_1 (\times 10^3)$ (the exponential constant expressing the postrotatory nystagmus decay) of 10 rotations in each of 5 individuals and for 4 different qualities V_1 , T_1 , V_2 and T_2 as in Figs. 1 and 2

	V_1		T_1		V_2		T_2	
	M	S	M	S	M	S	M	S
A. N.	-116.60***	31.91	84.10*	49.07	-22.10	22.01	-4.60	31.15
B. T.	-50.00***	19.39	43.60*	26.29	-1.50	17.43	4.50	16.88
C. L.	-71.90***	10.17	68.00*	27.77	-2.60	19.91	13.60	18.64
K. T.	-56.80***	12.11	27.00*	16.12	-9.80	13.30	-16.88	15.81
L. K.	-86.50***	37.50	28.90*	67.22	-37.20	63.81	-10.00	31.05



g. 2. The $e\log$ of nystagmus qualities as a function of time in postrotatory nystagmus in 5 normals. V_1 =speed of slow component; T_1 =duration of slow component;

V_2 =speed of fast component; T_2 =duration of fast component.

of the same magnitude as the acceleration. After 1 min the rotation was repeated. Ten nystagmus courses resulting from five such clockwise rotations were studied.

Recordings

The recordings of the patients were made in complete darkness and with the eyes of the patients open. The per- and post-rotatory nys-

tagmus was recorded with a d.c.-technique and the signals were taped on a Hewlett-Packard 3960 four-channel recorder. The nystagmus signal was then displayed on a mingograph with a recording paper fed at 10 cm/sec and with a scale-factor of $20^\circ=15$ mm. From this recording the velocities and durations of the fast and slow components of nystagmus were calculated.

Table II. Mean and spread in a_2 (the exponential constant that expresses $e\log$ the value of a nystagmus quality at peak stimulus) of 10 rotations in each of 5 individuals and for 4 different qualities

T_1 , V_2 and T_2 as in Figs. 1 and 2

	V_1		T_1		V_2		T_2	
	M	S	M	S	M	S	M	S
N.	3.962***	0.156	-1.563***	0.402	4.983**	0.217	-2.546***	0.241
T.	4.130***	0.255	-1.378***	0.258	5.168**	0.185	-2.484***	0.144
L.	4.192***	0.127	-2.141***	0.275	4.866**	0.257	-2.948***	0.161
T.	4.332***	0.199	-1.605***	0.167	4.889**	0.232	-2.158***	0.240
K.	3.935***	0.186	-1.497***	0.339	4.938**	0.365	-2.521***	0.234

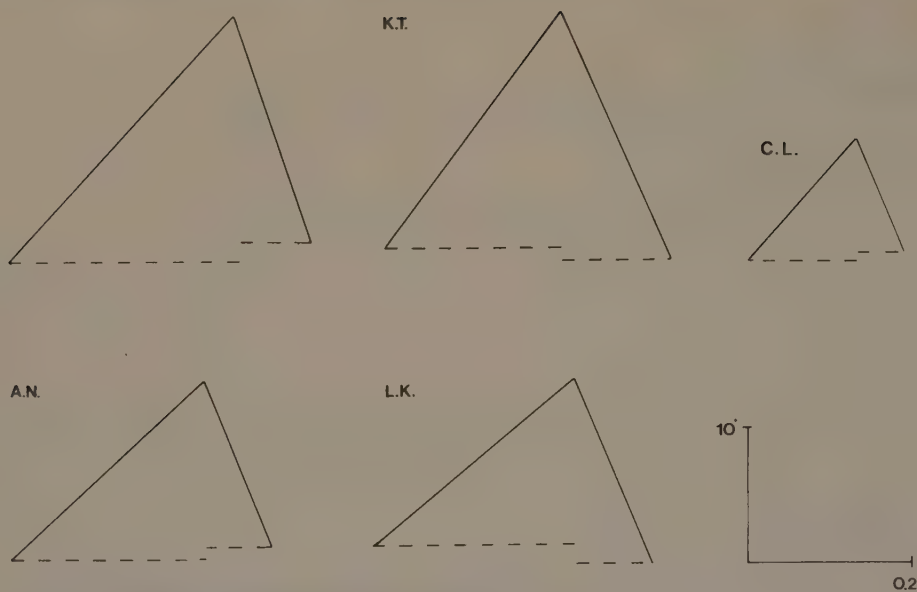


Fig. 3. The 'normated' nystagmus beats for each of the 5 patients. (The difference in appearance of each of the nystagmus beats is apparent.)

Statistical methods

In each of the 50 responses a_1 and a_2 for the four qualities were estimated by linear regression of the logarithmated material. S_r was determined as the residual spread (standard deviation) around the regression line. For each quality, differences between individuals were tested by means of analysis of variance (one-way classification with the factor 'individual' on five levels, giving an $F(4,45)$ test).

RESULTS

None of the nystagmus qualities showed any changes in a_1 , a_2 or S_r with repetition of the rotation.

Rate of postrotatory decay (a_1) of the four nystagmus qualities within the nystagmus responses

Differences between qualities. The decay within the nystagmus responses expressed as a_1 for each quality in 10 repeated responses and within each subject is accounted for in Table I and in Fig. 2. The different behaviour

of these qualities is apparent; for the velocity of the slow component a decrease, for the corresponding durations an increase, while there seems to be no clear-cut decrease or increase for the velocities and durations of the fast components.

Differences between individuals. A statistical analysis of a_1 for each of these qualities of the 5 subjects shows significant differences between individuals with respect to the velocity of the slow component (***). There was a significant difference between individuals as regards the duration of the slow component (*).

The 'log nystagmus quality at peak stimulation' (a_2)

From Fig. 2 the estimated initial value of the 'log of each quality' (a_2) can also be deduced. As the 'log for values of nystagmus qualities are rarely used in clinical connections we have also chosen to present the real values on the ordinate of Fig. 2. These values thus represent the values of each nystagmus quality at peak vestibular stimulation

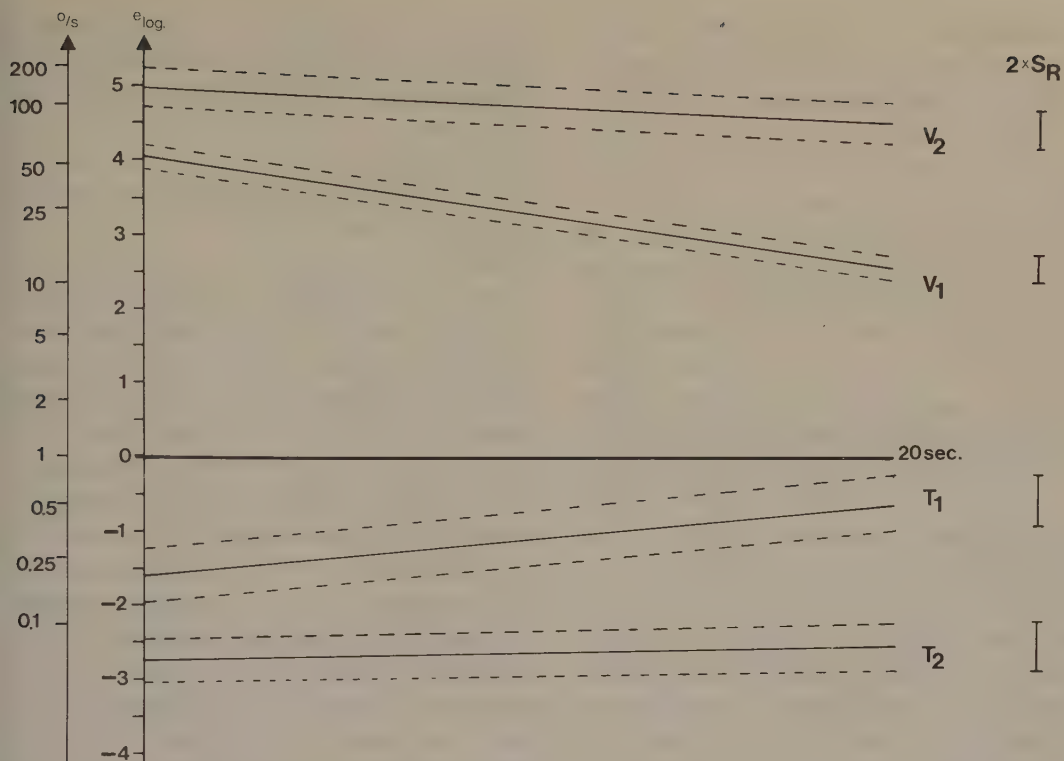


Fig. 4. The residual spread in semilogarithmic plotting of the four nystagmus qualities. The significantly smallest

residual spread is that of the speed of the slow component, V_1 , T_1 , V_2 and T_2 as in Figs. 1 and 2.

and are accounted for in Table II. On the basis of these findings a 'normated' nystagmus beat could be constructed for each subject (Fig. 3). Statistical differences between individuals with respect to these nystagmus qualities could be proved for all qualities.

Residual spread (S_r) around the calculated linear slope of each of the four nystagmus qualities

Difference between qualities. The spread from the calculated slope of each quality was determined for each rotation and each individual. Each rotation thus provides four values, one for each quality. The mean S_r for each quality is accounted for in Fig. 4:

0.175 for (V_1), 0.356 for (T_1), 0.264 for (V_2) and 0.340 for (T_2)

The smallest S_r of all 5 tested subjects was

thus found around the slope of the slow component.

Difference between individuals. Significant differences were found between individuals with respect to S_r in V_1 (**) and also in T_1 (*).

DISCUSSION

The procedure in these tests with accelerations following each other at intervals of only one minute, does not exclude interference between the postrotatory reaction and the postreaction shown by Mittermaier (1954). Consecutive rotations with long-lasting intervening periods of rest may, however, by prolonging the test introduce other sources of error (Stahle, 1957). Later it was also pointed out that sleepiness in the patient would tend to diminish the nystagmus (Collins et al., 1961).

As pilot studies did not indicate differences in any of our parameters (a_1 , a_2 , S_r) of any of the nystagmus qualities between the first and the following rotations the present procedure was finally chosen.

It must also be stressed that in this study we evaluated only the dysrhythmia expressed by the irregularity of nystagmus beats and not the type of dysrhythmia that results from intervening nystagmus pauses (Lidvall, 1961; Clément, 1970). The existence of pauses was considered, however, as each quality of the nystagmus beats was evaluated within its relation to the time axis.

a_1 , i.e. the rate of decay of the four nystagmus qualities

Comparison with earlier findings. The values determined for a_1 of V_1 agree with earlier findings by Groen (1956). He found a time constant for the vestibular system of 16 sec which would correspond to an a_1 constant of -0.06 compared with our findings of -0.12 to -0.05 . Hallpike & Hood (1953), using a different technique also to study the velocity of the slow component, found a time constant corresponding to an a_1 value of -0.1 .

Differences between qualities. The exponential constants a_1 for V_2 and T_2 were all relatively close to nil. This indicates that the velocities and durations of fast phases of nystagmus are rather independent of variations in vestibular stimulations and tend to assume the same values at the beginning as at the end of the postrotatory nystagmus responses. a_1 for V_1 was invariably negative and a_1 for T_1 invariably positive. These last two qualities may thus be more closely related to the exponentially decreasing vestibular stimulus in the postrotatory nystagmus response.

Differences between individuals. The significant differences between individuals with respect to a_1 (V_1) and also to a_1 (T_1) (Table I) indicate that the variation between individuals in the exponential decay of these qualities cannot be assumed to be an expression of pure random. It cannot be excluded that these

constants are expressions for personality-linked neuronal mechanisms in the central nervous system or in the physical properties of the cupula.

Initial value of the four nystagmus qualities and their exponential constants (a_2)

Comparison with earlier findings. The 'log of the initial value of each nystagmus quality, accounted for in Fig. 2, may be of less interest than the corresponding real values of the same figure and of Table II. The maximum velocities of slow components (53 – $78^\circ/\text{sec}$) match roughly only half of the values of the stimulus produced by rotation ($120^\circ/\text{sec}^2 \times 1 \text{ sec} = 120^\circ/\text{sec}$). This agrees with the k_e quotient of about 0.6 (Henriksson, 1955) and with the 'vestibular gain' of similar magnitude (Robinson, 1974).

The surprisingly low velocity of the fast component of about 170 – $190^\circ/\text{sec}$ is in contrast to an observation by Ron et al. (1972) but is recently confirmed by Henriksson et al. (1980) who found fast phase velocities significantly slower than the velocities of the voluntary saccades of corresponding amplitude.

Difference between individuals. As estimation of a_2 is based upon the whole series of postrotatory nystagmus beats this allows construction of a 'normated' nystagmus beat for each nystagmus reaction. This technique thus reduces errors to occasional variation in nystagmus sequences. The difference in a_2 between different individuals is expressed by the variation in appearance of the 'normated' nystagmus beats presented in Fig. 3. Thus it cannot be excluded that the appearance of nystagmus beats, like the rate of decay (a_1), may be connected to certain neuronal features, linked to the individual.

S_r , dysrhythmia as expressed by residual spread

Difference between qualities. The small residual spread in the velocity of slow component is to be expected, as the most im-

portant task of the vestibulo-ocular system should be to preserve an adequate speed of the slow component while the stability of the other nystagmus qualities in the nystagmus response may be of less importance. A more pronounced stability of this quality was also shown with a closely related technique used previously by Henriksson et al. (1976).

Difference between individuals. As a difference between individuals was found with respect to S_r for V_1 (**) as well as for T_1 (*) these expressions for dysrhythmia may be related to neuronal features linked to the individuals.

Of the twelve quantified parameters of the postrotatory nystagmus reactions determined by this analysis, at least eight presented values that proved significantly different within different individuals, (a_1 for V_1 and T_1 , a_2 for V_1 , T_1 , V_2 and T_2 as well as the residual spread S_r for V_1 and T_1). In the four remaining parameters, no significant coupling to the individual was found.

Although the clinical value of the present technique is not yet proven, it does provide normated values for each nystagmus quality, expressions for the postrotatory exponential trends of these qualities, as well as expressions for the rhythm of these qualities. As techniques for on-line analysis of nystagmus now seem to be about to be introduced even in clinical work (Honrubia et al., 1971; Anzaldi & Mira, 1975; Michaels & Tole, 1977; Ranacher, 1977; Buizza et al., 1978), it has been our intention to suggest our type of processing of the nystagmus data.

Efforts to chart the extent to which these parameters can be used for clinical purpose should now be undertaken.

SUMMARY AND CONCLUSION

Computer-assisted analysis of postrotatory nystagmus was carried out by determining the exponential constants for velocities (V_1 and V_2) and durations (T_1 and T_2) of slow and fast components of nystagmus. The dysrhythmia

of the nystagmus response was quantified by determining the residual spread in a semi-logarithmic plot of each of the four nystagmus qualities.

This analysis indicated an exponential decrease of the slow component and a lengthening of the duration of the slow component, but no such changes for the fast component.

The exponential decay also presented significant differences between individuals in the velocity and the duration of the slow component, but no such differences for the fast component. The initial values of all the four nystagmus qualities showed significant differences between individuals.

The residual spread was regarded as an expression of dysrhythmia and was smallest for the velocity of the slow component.

The analysis presented here was meant to facilitate application to on-line analysis of nystagmus for future clinical use.

ZUSAMMENFASSUNG

Bei 5 gesunden Personen wurden die postrotatorischen exponentiellen Konstanten für jede der vier Nystagmusqualitäten Geschwindigkeit und Dauer der schnellen und langsamen Komponente zusammen mit ihrer residualen Streuung (S_r) bei semilogarithmischer Darstellung bestimmt. Der Konstantenwert der postrotatorischen Reaktionsabnahme zeigte bei der Geschwindigkeit der langsamen Komponente einen Abfall und bei der Dauer der langsamen Komponente einen Anstieg, beide mit signifikanten interindividuellen Differenzen. Die korrespondierenden Werte der schnellen Komponente hingegen wiesen weder systematische Veränderungen bei den postrotatorischen Reaktionen noch interindividuelle Differenzen auf. Die bei maximaler Stimulation bestimmte Komponente zeigte Differenzen zwischen den einzelnen Individuen bei allen vier Nystagmusqualitäten, während die residuale Streuung nur bei den beiden Qualitäten der langsamen Phase interindividuelle Differenzen aufwies. Das vorgestellte Verfahren zur Beschreibung postrotatorischer Nystagmusreaktionen unter Verwendung von zwei exponentiellen Konstanten für jede der obengenannten Qualitäten wird für zukünftige „on-line“-Nystagmusanalysen gebraucht.

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CLINICAL EVALUATION OF DYSRHYTHMIA OF POSTROTATORY NYSTAGMUS

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ABSTRACT

Postrotatory responses of nystagmus were analysed in an exponential model by utilizing linear regression analysis. Four nystagmus qualities (velocity and duration of slow and fast phases) were studied in 10 patients with vestibular peripheral lesions, 10 patients with frontal lobe lesions and 10 patients with brain-stem lesions, together with 10 control subjects. In addition, pauses during the responses were quantified. Patients with frontal lobe lesions differed from other groups by scoring higher values of slow phase velocity and by exhibiting more pauses. The time constant was significantly shorter in patients with brain-stem lesion than in any other group. As regards other qualities, e.g. slow phase duration and fast phase velocity, or duration, no differences were observed. The pathological dysrhythmia may therefore be presented as changes in the gain and time constant of slow phase velocity as well as in pauses during nystagmus. Since all these changes may be encountered in normal subjects, one should be cautious in interpreting these changes as being pathological in each individual case.

Prominent changes in nystagmic rhythm in the caloric test have been assumed to stem from a lesion within the central nervous system (Leidler, 1939; Aschan et al., 1956; Riesco-MacClure & Stroud, 1960). However, vestibular nystagmus in a normal subject may also be variable and irregular (McLay et al., 1957; Clément, 1970; Fluor, 1982). Clément (1970) showed that the different patterns of dysrhythmia, such as dysmetria, petit ecriture, salvos, group formations and secondary phase of nystagmus, all occur in normal subjects and can be attributed to the attention span of the subject. The clinical value of caloric dysrhythmia has been further challenged by other researchers on account of the character of caloric stimulation (Hood, 1973; Jongkees, 1973; Baloh & Honrubia, 1979).

In the rotatory test too, which is considered to be far more physiologic than the caloric test, different patterns of dysrhythmia have been observed in the regulation of nystagmus. Honrubia et al. (1980) described prominent amplitude variations of nystagmus which could be connected with the site of the lesion. According to these authors, in the presence of a central vestibular lesion the nystagmus will be disorganized and the fast components occur in a random fashion, especially when the lesion involves the cerebellum. In only a few reports, however, has dysrhythmia of nystagmus been analysed quantitatively. Buizza et al. (1978) and Schmid (1982) reported that dysrhythmia of nystagmus will appear as a deviation in the distribution of the intersaccadic intervals or as an amplitude variation between successive fast components.

Since the course of the postrotatory nystagmus - quantified either as subjective rotation magnitude, or velocity of the slow phase - decays in a logarithmic manner (Egmond & Groen, 1955) the smoothness of the responses has been studied also by fitting a linear regression function to the response course (Börjesson et al., 1981). Hence, to each nystagmus component, e.g. velocity or duration of slow and fast phase, an exponential model has been adapted (Henriksson et al., 1976). Furthermore, in the individual response pattern the extent of variation from beat to beat and applicability of the response to the model has been regarded as a sign of nystagmic dysrhythmia in normal subjects (Börjesson et al., 1981).

The purpose of the present work was to adapt the exponential model (Börjesson et al., 1981) to the postrotatory nystagmus responses of three groups of patients. In addition the occurrence of pauses in nystagmus is analysed.

MATERIAL AND METHODS

Subjects

Ten normal subjects, aged 21 to 62 years, were recruited for the determination of normative values. Five of them had been employed in the recording of individual responses in an earlier study (Börjesson et al., 1981). All the subjects were healthy, with normal neuro-otological findings and were free from any illness that might have interfered with their performance during the test.

Thirty patients with various neurological diseases were selected for this study. They were divided into three groups depending on the site of lesion.

Group 1

Ten patients with a peripheral vestibular lesion. They were screened by a neurologist, and otoneurological tests indicated that they were free from central involvement. Eight had vestibular neuronitis, one had acute labyrinth malfunction due to middle ear infection and one had Ménière's disease. These patients were considered to represent a group of peripheral vestibulopathy. Their mean age was 52.9 years (range 35-69 years).

Group 2

Ten patients with dyspraxia of speech (Darley et al., 1975). Each had a lesion in Broca's speech area, located in the vicinity of the left frontal eye field. Hence, they represented patients with a lesion in the frontal lobe. Six patients had cerebral infarctions, one had been injured in a traffic accident and 3 had a degenerative disease of Alzheimer type. Some of the patients have been included in an earlier study (Dahlen et al., 1980). Their mean age was 56.3 years (range 25-73 years).

Group 3

Ten patients with a brain-stem lesion. Six of them suffered from brain-stem infarctions. Three had ischemia of the brain stem, with localized clinical findings; one had a pontine glioma. Their mean age was 63.6 years (range 45-76 years).

Methods

DC electro-oculograms of horizontal and vertical eye movements were recorded simultaneously with an ink-jet recorder (Mingograph M 81, Siemens Elema, Stockholm, Sweden). A 15-Hz filter was used and the paper was fed at 100 mm/sec. The accuracy of the interpretation in horizontal direction allowed 1° for amplitude and 10 msec for time events.

The rotatory test was carried out by accelerating the subject in the dark to a constant angular velocity of 120°/sec within

1 sec. After 60 sec the chair was brought to a standstill within 1 sec and the postrotatory response, to both clockwise and counterclockwise rotation was measured.

The velocity, amplitude and duration of the slow and fast phases of nystagmus were derived from the recording by hand scoring. The data was fed into a computer and a linear regression analysis was performed on a semilogarithmic scale. For each postrotatory response four variables of nystagmus, viz. velocity of slow phase, duration of slow phase, velocity of fast phase and duration of fast phase of nystagmus, were related to the time course of the response. In the linear regression analysis, intercept (intersection of regression line with y-axis), regression coefficient (slope of the regression line) and standard error for residuals (S_r) were determined. As indicated in the previous work, S_r was a good measure of dysrhythmia in normal subjects (Börjesson et al., 1981).

The missing periods were estimated by interpolating the surface area of the nystagmus-free period from the exponential decay of slow phase velocity. Thus, the slow-phase amplitudes were determined with respect to the nystagmus amplitude that the eye would have passed if there had been no absence of nystagmus. The missing amplitudes were accumulated and the results expressed as a percentage of estimated total amplitude.

Statistics

The statistical significance of differences in intercept, regression coefficient and standard error of regression between different groups was analysed with the Kruskal-Wallis test (Siegel, 1956). The differences were considered statistically significant when $p < 0.05$.

RESULTS

1. Adaptation of the exponential model to the velocity (V_1) and duration (T_1) of the slow phase of nystagmus and to the velocity (V_2) and duration (T_2) of the fast phase

Patients with a frontal lobe lesion tended to respond with higher slow phase velocities than patients in the other groups (Fig. 1). At the intercept of the regression line of V_1 , statistically significant differences were observed within the four groups studied ($H(3) = 8.89, p < 0.05$). In pairwise comparison, however, only the difference between the patients with a frontal lobe lesion vs. control subjects was statistically significant ($H(1) = 9.61, p < 0.05$).

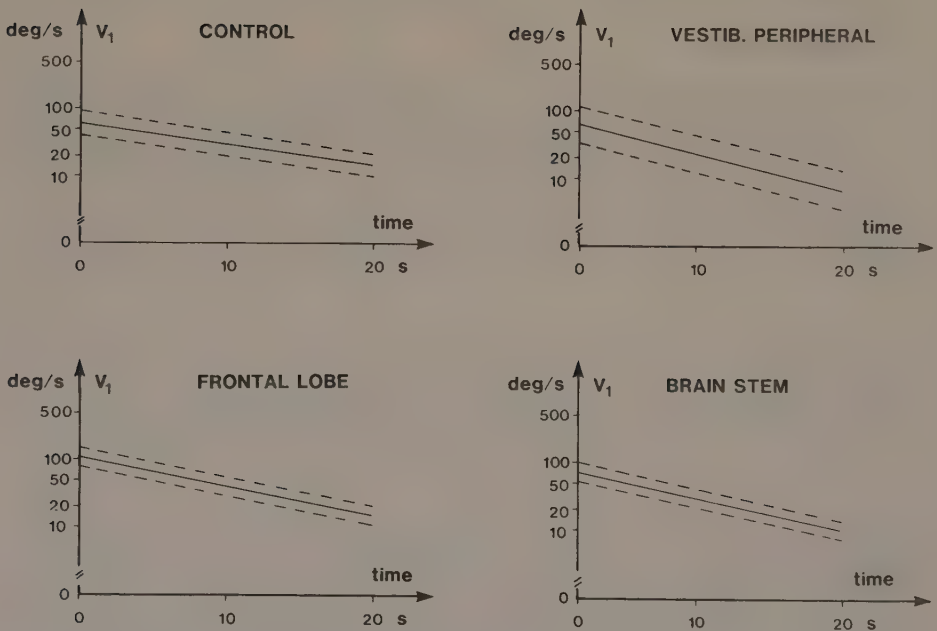


Fig. 1. Regression lines fitted to exponential course of slow phase velocity (V_1) of nystagmus in normal subjects and three groups of patients. Standard error for regression is depicted by broken lines.

In the regression coefficients of V_1 , describing the time constant for the postrotatory response, the groups of subjects studied differed significantly from each other ($H(3) = 10.88$, $p < 0.05$). The patients with brain-stem disorders showed a significantly steeper response course and lower regression coefficient values than normal subjects ($H(1) = 7.61$, $p < 0.05$).

In the adaptation of the exponential model to T_1 (Fig. 2) no significant differences between the four groups of subjects were observed with respect to intercepts or to regression coefficients.

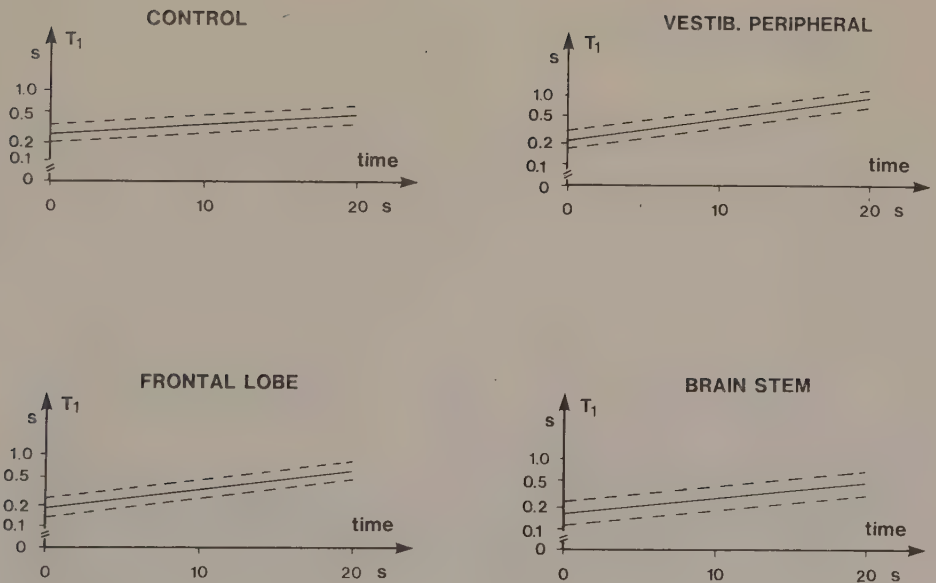


Fig. 2. Regression lines fitted to exponential course of duration of the slow phase (T_1) of nystagmus in normal subjects and three groups of patients. Standard error for regression is depicted by broken lines.

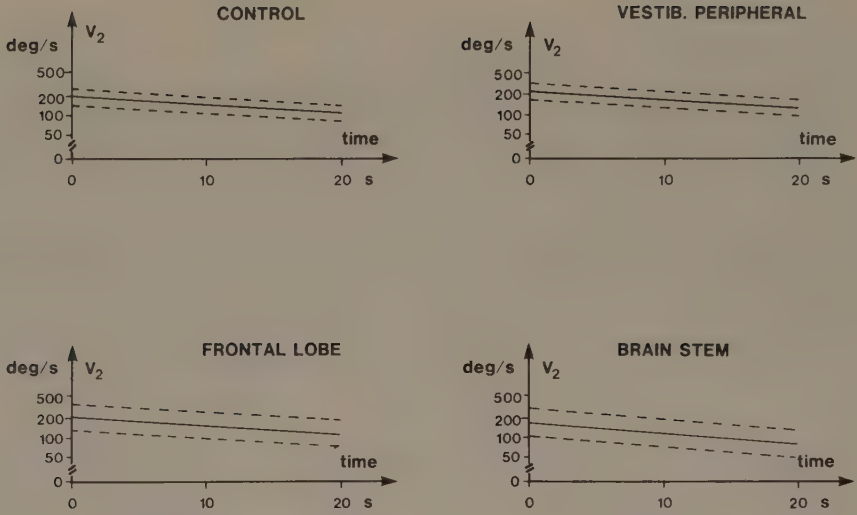


Fig. 3. Regression lines fitted to exponential course of fast phase velocity (V_2) of nystagmus in normal subjects and three groups of patients. Standard error for regression is depicted by broken lines.

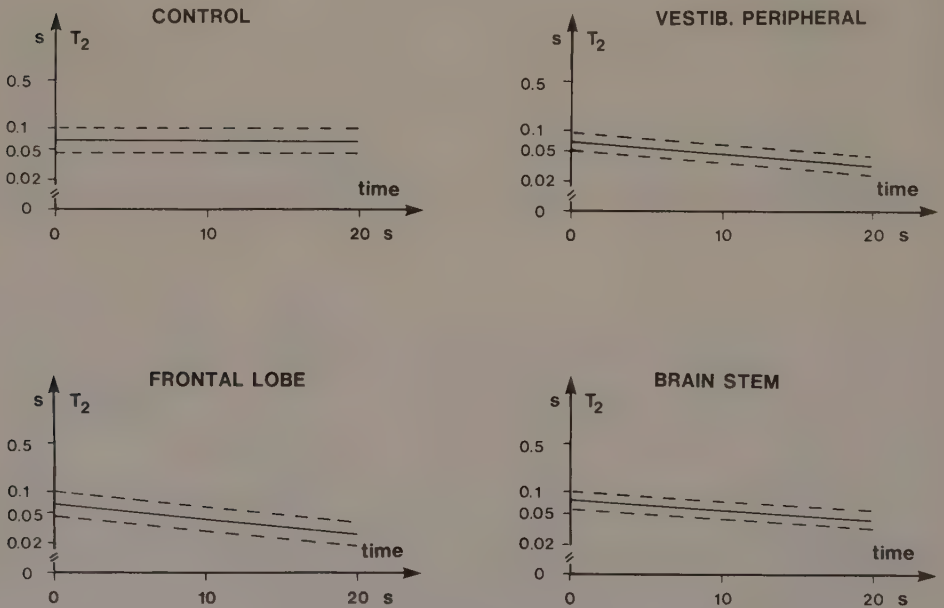


Fig. 4. Regression lines fitted to exponential course of duration of the fast phase (T_2) of nystagmus in normal subjects and three groups of patients. Standard error for regression is depicted by broken lines.

In the exponential adaptation, neither V_2 (Fig. 3) nor T_2 (Fig. 4) differed significantly between any of the groups studied with respect to the intercept or to regression coefficient.

2. Standard error for residuals (S_r) of the exponential model

The mean values of S_r were determined for the different groups of patients and control subjects. The values for V_1 , T_1 , V_2 , and T_2 are set out in Figs. 1, 2, 3 and 4, respectively. The mean values of S of the control subjects are of about the same order as in the three groups of patients. No statistically significant differences were observed between the different groups for any of the nystagmus variables studied.

3. Disappearance of nystagmus in postrotatory nystagmus response

Fig. 5 gives the percentage of missing amplitudes from estimated total amplitude of nystagmus. The largest number of interruptions occurred in the patients with frontal lobe lesions ($H(1) = 10.32$, $p < 0.01$). The difference between control subjects and other groups of patients was not significant.

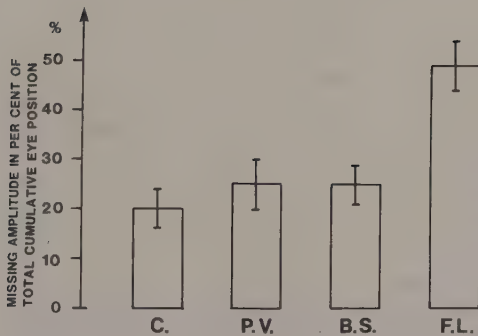


Fig. 5. Pauses in nystagmus expressed as missing amplitudes as a percentage of total cumulative eye position in normal subjects and three groups of patients. Means and standard error of mean are depicted. Abbreviations: C = control. P.V. = peripheral vestibular, B.S. = brain stem, F.L. = frontal lobe.

DISCUSSION

In the present study the postrotatory responses were analysed in an exponential model by utilizing a linear regression analysis. The model was applied to four nystagmus qualities and three different groups of patients were compared with normal subjects. In addition, the pauses in the postrotatory nystagmus were quantified by determining the total missing amplitudes of nystagmus for the responses.

The results indicate that in the postrotatory nystagmus response, a significant response variation occurs even in normal subjects and that only a few variables, for instance maximum value and response decay of V_1 , differed significantly between the patients and the normal subjects. Poor adaptation of the model and a paucity of differences was evident in the fast components of nystagmus. The present findings support the concept of the basic need for high stability of the vestibulo-ocular reflex arch. Furthermore, since the fast phase of nystagmus is not produced in the end organ but processed in the central vestibular system, fast phase velocity and duration gave a poor fit in the model.

1. Application of exponential model to various qualities of nystagmus

The concept of the exponential model used in the present work was originally presented by van Egmond et al. (1949). In their model the momentary deviation of the cupula (ξ) was thought to be related in an exponential way ($\xi = e^{a_1 t + a_2}$) to the returning velocity of the cupula (a_1) at a given time point (t) and to maximum value of the cupular deviation (a_2). Empirically, the deviation of the cupula was related to the velocity of the slow phase (V_1) (Egmond & Groen, 1955). A linear transfer function was hypothesized between cupular deviation and eye velocity; $\xi = C \cdot V_1$, in which the coefficient (C) describes the gain in transfer function. Since the transfer function between cupula and eyes behaves exponentially ($C \cdot V_1 = e^{a_1 t + a_2}$), the responses can be visualized on a semilogarithmic scale by plotting nystagmus velocities against time. The values will be aligned and the relationship can be studied by linear regression analysis. Thus, the intercept in the present results is related to exponential constant a_2 in van Egmond and co-workers' model and describes the response maximum. The regression coefficient is related to the exponential constant a_1 which describes the time constant of the nystagmus. Theoretically, dysrhythmia might appear as changes in the intercept, regression coefficient, or standard error for residuals.

In the present study only a few significant differences were found when the exponential model was applied. Our results support the findings of Schalén et al. (1982) who reported that in the lesions affecting the central vestibular system the

postrotatory responses usually remain intact, despite severely disturbed voluntary eye movements. Furthermore, noticeable changes in the time constant of nystagmus are rare and occur in connection with relatively large lesions affecting the brain stem (Blair & Gavin, 1981).

Allegedly, the vestibular end organ does not provide any information regarding the duration of slow phase. Nevertheless, the exponential model finds a good fit also in T_1 . Since T_1 is closely correlated to V_1 (Pyykkö & Dahlen, 1983) the exponential model applied to this component presumably tests the common variance which it shares with the velocity signal. Consequently, the aptness of T_1 in the linear regression analysis, expressed as S_r , was not as good as for V_1 and may explain the paucity of significant differences in this nystagmus component.

Nevertheless, we were unable to show any significant correlation between V_2 or T_2 and the temporary course of nystagmus. Although the model should be restricted to those components of nystagmus with an exponential behaviour, we still found it worthwhile to explore this possibility. The lack of any apparent correlation in V_2 and T_2 in the model may be due to the fact that V_2 depends on the amplitude of the fast phase (cf. Pyykkö et al., 1981) and that the amplitude varies widely during the response. The pathological variation in the fast phase of nystagmus might, however, appear in sequential analysis of successive fast phases (Buizza et al., 1978).

2. Smoothness of nystagmus response expressed as standard error for residuals (S_r)

Allegedly, the lack of changes in S_r of V_1 may be attributed to the high stability of the vestibulo-ocular reflex arch after various types of lesion. Consistently in V_1 the spread of nystagmus around the regression line was comparatively small when compared with other nystagmus components and about the same irrespective of the changes in the gain or in the extent of the periodic absence of nystagmus in the present study.

Since S_r measures the average error for the whole response, our result does not exclude the possibility that a dysrhythmia of nystagmus with respect to variation in V_1 or V_2 might derive from short and temporary changes in the velocity. In fact, the data provided by Fluor (1982) indicate that in some cases this kind of dysrhythmia of V_1 does exist. A quantitative analysis of temporary deviation in rhythm is difficult and does not, according to Fluor (1982), distinguish between healthy and disabled subjects.

3. Pauses in the postrotatory response

Short periods of nystagmus suppression have been considered to be a normal finding in order to suppress excessive activity of the vestibular system (Fluor, 1982). In the present study too, nystagmus-free periods covered about 20 per cent of total

amplitude of nystagmus in normal subjects. However, nystagmus-free periods were found far more often among patients with a frontal lobe lesion. This finding was rather unexpected, since these patients had in most instances a very intensive nystagmus. The faulty nystagmus response among the frontal lobe patients may derive from a lesion in the frontal eye field, located in the prefrontal cortex (Penfield & Rasmussen, 1950).

This area contains a population of neurons which respond to various forms of nystagmus, voluntary eye movements and movements of the head (Bizzi, 1968; Bizzi & Schiller, 1970; Goldberg & Bushnell, 1981). Enhanced vestibular responses in the present study may be regarded as stemming from a dysfunction in a neural circuitry controlling the vestibular output. Moreover a dysfunction in the frontal eye field may also explain the more frequent pauses of nystagmus among these patients.

4. Conclusion

Pathological dysrhythmia in the present results could be detected by absence of nystagmus, increase in maximum velocity and decreased time constant of the slow phase of nystagmus. Since all these changes could be encountered to some extent also among the control subjects, caution should be taken when interpreting the nystagmogram as pathological with respect to these changes in individual cases.

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INTRABEAT RELATIONSHIP OF POSTROTATORY NYSTAGMUS IN NORMAL
SUBJECTS

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ABSTRACT

Intrabeat relationships between duration, amplitude and velocity of the slow phase of nystagmus and between amplitudes of the fast and slow phase of nystagmus were analysed from postrotatory responses in 10 normal subjects, using linear regression analysis. For 5 subjects, the tests were repeated five times. A significant correlation was found between velocity and amplitude of the slow phase as well as between velocity and duration of the slow phase in all subjects. These intrabeat relationships were repeatable and representative for each individual. Highly significant correlation was found between amplitudes of the slow and fast phases of nystagmus in all subjects. No interindividual differences in these variables could be observed. The results indicate that the end-point of the slow phase of vestibular nystagmus in darkness is controlled by positional and durational corollary circuitries. The positional signal in displacement circuitry is probably derived by integration of the velocity signals from the labyrinths. The durational circuitry is presumably more dominant at high nystagmus velocities in order to permit sufficient time for fixation.

INTRODUCTION

Angular acceleration of the head delivers a continuous array of impulses to the vestibular nerve (Goldberg & Fernández, 1975) and the vestibular nuclei (Fuchs & Kimm, 1975). At the site of the oculomotor nuclei the velocity information is combined with positional information leading to rhythmic activation of the external eye muscles, resulting in the slow and fast phases of nystagmus.

It is believed that the fast phase resets the position of the eyes at the end of the slow phase and provides a new fixation point. In addition, the fast phase anticipates the movement of the head (Donaghy, 1980). The velocity of the slow phase controls to some extent the end-point of nystagmus, but the position of the eyes in the orbit seems, according to Lau et al. (1978), to be a far more important factor in triggering the fast phase of nystagmus. Nevertheless, Bergstedt (1973) concluded that in addition to the positional signal from the eyes, durational information is also included in the determination of the end-point of nystagmus, and changes in nystagmus patterns result from variations in these nystagmus variables.

The present knowledge of reciprocal relations between duration, amplitude and velocity of nystagmus does not permit an understanding of the temporal and positional control of eye movement during nystagmus. The variability of the velocity, amplitude and duration between consequent slow and fast phases during the same nystagmus response is often denoted as dysrhythmia (cf. Clément, 1970). However, the degree of the possible dysrhythmia has not been studied quantitatively in intrabeat analysis in normal subjects.

The aims of the present study were to analyse the possible mechanisms by which the slow phase end-point is determined in postrotatory responses and to find out to what extent the amplitudes of slow and fast phases of nystagmus reveal deviation from the normal rhythm.

MATERIAL AND METHODS

Ten normal volunteers (mean age 41.4 years, range 21-62) served as subjects in this study. They had no history of vestibular disorders and a routine otoneurological investigation proved normal.

The eye movements were analysed using a standard electro-oculographic technique (Henriksson et al., 1980). The horizontal eye movements were recorded binocularly and the vertical eye movements from each eye separately. The positional signal of the eyes was recorded with an ink-jet recorder (Mingograph M 82, Siemens Elema, Stockholm, Sweden). An upper cut-off frequency of 15 Hz with infinite time constant was used.

The subjects were exposed to the Bárány rotatory test. The chair was accelerated within one second to a speed of 120°/s. The rotation lasted 60 s, after which the chair was decelerated to a standstill within one second. Responses to clockwise and counterclockwise rotation were recorded. The analysis was limited to per-rotatory responses. For 5 subjects, tests were performed five times to study the variability of successive responses.

In the postrotatory nystagmus for each nystagmus beat, velocity, amplitude, and duration were calculated by manual scoring for the slow as well as fast phase. To analyse the intrabeat variation between different qualities within the nystagmus beat, the data were fed into a minicomputer (PDP 11-23, Digital Equipment). Interactive programs were developed by which linear regression analysis between different variables could be performed. The program allowed a comparison of values on a non-logarithmic or on a logarithmic scale.

Statistics

The statistical significance of the correlation coefficients was evaluated with Student's t-test. In the case of dependence of intercorrelations between the variables, the partial correlation coefficients were determined (Edwards, 1979). In repeated tests, the difference between subjects was tested with Friedman's analysis of variance (Siegel, 1956). The difference between correlation coefficients obtained in linear regression analysis on non-logarithmic vs. logarithmic scales was tested with the Kruskal-Wallis test (Siegel, 1956). The difference was considered statistically significant when $p < 0.05$.

RESULTS

1. Relationship between velocity (V_1) and amplitude (A_1) of slow phase of nystagmus

Fig. 1 displays the mean value of the slow-phase velocity (V_1) at amplitude (A_1) together with regression line between these variables in 10 normal subjects. A linear regression analysis performed between A_1 and V_1 showed a highly significant correlation between the parameters ($r(861) = 0.523$, $p < 0.001$). The regression coefficient between V_1 and A_1 for the group was 1.83 with 95% confidence limits of 1.61 to 2.05 and with a standard error for regression of 17.98°/s.

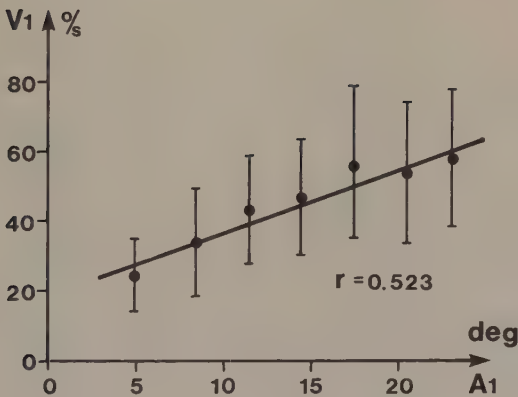


Fig. 1. Intrabeat relationship between velocity of slow phase (V_1) and amplitude of slow phase (A_1) of nystagmus. Mean values and standard deviations for various amplitude classes are shown. In addition, the linear regression line ($y = 18.42 + 1.8 x$, $SR = 17.97$, $n = 861$) describing the connection between V_1 and A_1 ($r = 0.523$) is depicted in the figure.

To study whether a logarithmic conversion of one or both of the variables would yield a better correlation the variables were examined after logarithmic conversion had been performed. When both A_1 and V_1 were converted to a logarithmic scale, a marginally better overall correlation was obtained ($r(861) = 0.579$, $p < 0.001$). However, in individual subjects the correlation between V_1 and A_1 improved in 5 subjects and worsened in 5 subjects. The improvement of logarithmic conversion of the parameters in the group was not statistically significant ($H(3) = 0.763$, $p = n.s.$). Therefore, linear regression analysis using non-logarithmic scales was applied.

Table I. Correlation coefficients (r) for A_1 and V_1 in different subjects, levels of statistical significance, and numbers of observations (n) in parentheses.

Subj. ...	1	2	3	4	5	6	7	8	9	10
Test order	$r = 0.613$ ($n = 50$)	$r = 0.577$ ($n = 92$)	$r = 0.185$ ($n = 99$)	$r = 0.819$ ($n = 153$)	$r = 0.625$ ($n = 50$)	$r = 0.599$ ($n = 41$)	$r = 0.784$ ($n = 149$)	$r = 0.256$ ($n = 121$)	$r = 0.383$ ($n = 76$)	$r = 0.837$ ($n = 30$)
I										
II	$r = 0.669$ ($n = 50$)	$r = 0.361$ ($n = 87$)	$r = 0.066$ ($n = 87$)	$r = 0.434$ ($n = 135$)	$r = 0.673$ ($n = 52$)					
III	$r = 0.464$ ($n = 59$)	$r = 0.341$ ($n = 104$)	$r = 0.441$ ($n = 102$)	$r = 0.588$ ($n = 107$)	$r = 0.708$ ($n = 46$)					
IV	$r = 0.391$ ($n = 47$)	$r = 0.012$ ($n = 66$)	$r = 0.122$ ($n = 87$)	$r = 0.373$ ($n = 117$)	$r = 0.406$ ($n = 28$)					
V	$r = 0.569$ ($n = 45$)	$r = 0.585$ ($n = 123$)	$r = 0.423$ ($n = 104$)	$r = 0.550$ ($n = 75$)	$r = 0.333$ ($n = 36$)					
Tot. I-V	$r = 0.453$ ($n = 251$)	$r = 0.425$ ($n = 472$)	$r = 0.291$ ($n = 479$)	$r = 0.613$ ($n = 587$)	$r = 0.650$ ($n = 212$)					

$x = p < 0.05$, $xx = < 0.01$, $xxx = p < 0.001$

In individual testing, 9 out of 10 subjects showed a statistically significant correlation between these variables (Table I), whereas in one subject the correlation was less significant ($r(99) = 0.185^*$, $p < 0.05$). The variability in individual responses was examined by performing the test five times for the same subjects. The correlation coefficients between V_1 and A_1 showed rather less intra-individual variability than interindividual variability (Table I). In general, a consistent individual response pattern was found for the subjects ($\chi^2(3) = 8.64$, $p = 0.05$).

2. Relationship between velocity (V_1) and duration (T_1) of slow phase of nystagmus

Fig. 2 shows the mean values and standard deviations of the slow phase velocity (V_1) at given durations of the slow phase (T_1) together with a regression line between these variables in 10 normal subjects. The correlation coefficient between V_1 and T_1 is highly significant ($r(861) = -0.470$, $p < 0.001$). The regression coefficient between the variables was -0.0045 with 95% confidence limits of -0.0039 to -0.0051 and with a standard error for regression of $0.18^\circ/\text{s}$.

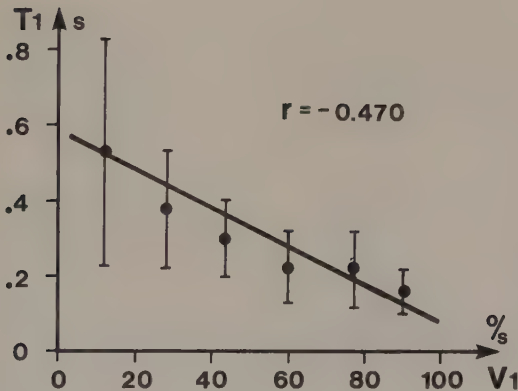


Fig. 2. Intrabeat relationship between velocity of slow phase (V_1) and duration of slow phase (T_1) of nystagmus. Mean values and standard deviations for different amplitude classes are shown. A linear regression line ($y = 0.53 - 0.0045 x$, $SR = 0.18$, $n = 861$) describing the connection between V_1 and T_1 ($r = -0.470$) is depicted in the figure.

After logarithmic conversion of one or both variables the relationship between V_1 and T_1 showed a tendency to a higher correlation coefficient ($r(861) = -0.562$, $p < 0.001$). In 6 subjects, when both variables were studied on logarithmic scales, the relationship between V_1 and T_1 was improved, whereas in 4 it was worsened. The improvement in relationship after logarithmic conversion was statistically not significant ($H(3) = 1.10$, $p = \text{n.s.}$). Consequently, non-logarithmic regression analysis was applied.

Table II. Correlation coefficients (r) for V_1 and T_1 in different subjects, levels of statistical significance, and numbers of observations (n) in parentheses.

Subj..	1	2	3	4	5	6	7	8	9	10
Test order	$r = -0.288$ ($n = 50$)	$r = -0.502$ ($n = 92$)	$r = -0.774$ ($n = 99$)	$r = -0.415$ ($n = 153$)	$r = -0.359$ ($n = 50$)	$r = -0.600$ ($n = 41$)	$r = -0.693$ ($n = 149$)	$r = -0.660$ ($n = 121$)	$r = -0.513$ ($n = 76$)	$r = -0.358$ ($n = 30$)
I										
II	$r = -0.580$ ($n = 50$)	$r = -0.579$ ($n = 87$)	$r = -0.597$ ($n = 87$)	$r = -0.571$ ($n = 139$)	$r = 0.056$ ($n = 52$)					
III	$r = -0.440$ ($n = 59$)	$r = -0.432$ ($n = 104$)	$r = -0.526$ ($n = 102$)	$r = -0.455$ ($n = 107$)	$r = 0.139$ ($n = 46$)					
IV	$r = -0.736$ ($n = 47$)	$r = -0.641$ ($n = 66$)	$r = -0.451$ ($n = 87$)	$r = -0.545$ ($n = 117$)	$r = -0.210$ ($n = 28$)					
V	$r = -0.514$ ($n = 45$)	$r = -0.502$ ($n = 123$)	$r = -0.505$ ($n = 104$)	$r = -0.372$ ($n = 75$)	$r = -0.473$ ($n = 36$)					
	$r = -0.495$ ($n = 251$)	$r = -0.501$ ($n = 472$)	$r = -0.539$ ($n = 479$)	$r = -0.489$ ($n = 587$)	$r = -0.060$ ($n = 212$)					

$x = p < 0.05$, $xx = p < 0.01$, $xxx = p < 0.001$

In individual testing, all subjects showed a statistically significant correlation between V_1 and T_1 (Table II). In individual responses the relationship between these variables showed good repeatability when conducted five times in the same subjects (Table II). In general, a subject showing a good vis-à-vis poor correlation performed the same manner in repeated tests ($\chi^2 (3) = 9.12, p < 0.05$).

3. Relationship between amplitude (A_1) and duration (T_1) of slow phase of nystagmus

An apparently good correlation was found between A_1 and T_1 ($r(861) = 0.350, p < 0.001$). Both of the variables A_1 and T_1 are interrelated with V_1 and consequently their common variation with V_1 could explain their relationship. Partial correlation coefficients were therefore calculated. In fact, the partial correlation coefficient between A_1 and T_1 ($r = 0.02, p = \text{n.s.}$) indicated that, as expected, the common variation that both A_1 and T_1 share with V_1 was the reason for the correlation found in linear regression analysis. The partial correlation coefficients for the relationship between V_1 and A_1 (T_1 kept constant) was 0.493 ($p < 0.001$) and between V_1 and T_1 (A_1 kept constant) 0.471 ($p < 0.001$).

4. Relationship between slow phase amplitude (A_1) and fast phase amplitude (A_2) of nystagmus

Fig. 3 shows the mean values and standard deviation of A_2 , when plotted against A_1 as well as a regression line between these factors in 10 normal subjects. A highly significant relationship between A_1 and A_2 ($r(861) = 0.678, p < 0.001$) was demonstrated by linear regression analysis. The mean regression coefficient was 0.72, with 95% confidence limits of 0.67 to 0.77 and the standard error of regression was 4.69° .

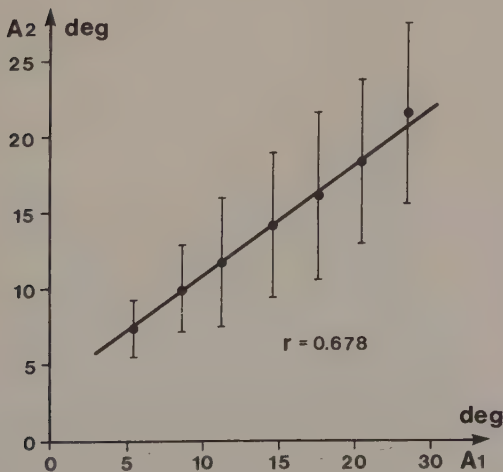


Fig. 3. Intrabeat relationship between amplitude of slow phase (A_1) and amplitude of fast phase (A_2) of nystagmus. Mean values and standard deviations for different amplitude classes are shown. A linear regression line ($y = 3.68 + 0.72 x$, $SR = 4.69$, $n = 861$) describing the connection between A_1 and A_2 ($r = 0.678$) is depicted in the figure.

Table III. Correlation coefficients (r) for A_1 and A_2 in different subjects, levels of statistical significance, and numbers of observations (n) in parentheses.

Subj.	1	2	3	4	5	6	7	8	9	10
Test order	$r = 0.487$ ($n = 50$)	$r = 0.660$ ($n = 92$)	$r = 0.582$ ($n = 99$)	$r = 0.784$ ($n = 153$)	$r = 0.708$ ($n = 50$)	$r = 0.333$ ($n = 41$)	$r = 0.516$ ($n = 149$)	$r = 0.454$ ($n = 121$)	$r = 0.417$ ($n = 76$)	$r = 0.712$ ($n = 30$)
I										
II	$r = 0.552$ ($n = 50$)	$r = 0.349$ ($n = 87$)	$r = 0.605$ ($n = 87$)	$r = 0.453$ ($n = 135$)	$r = 0.755$ ($n = 52$)					
III	$r = 0.603$ ($n = 59$)	$r = 0.627$ ($n = 104$)	$r = 0.567$ ($n = 102$)	$r = 0.569$ ($n = 107$)	$r = 0.662$ ($n = 46$)					
IV	$r = 0.424$ ($n = 47$)	$r = 0.186$ ($n = 66$)	$r = 0.739$ ($n = 87$)	$r = 0.740$ ($n = 117$)	$r = 0.518$ ($n = 28$)					
V	$r = 0.743$ ($n = 45$)	$r = 0.263$ ($n = 123$)	$r = 0.684$ ($n = 104$)	$r = 0.551$ ($n = 75$)	$r = 0.417$ ($n = 36$)					
Tot. I-IV	$r = 0.613$ ($n = 251$)	$r = 0.411$ ($n = 427$)	$r = 0.667$ ($n = 479$)	$r = 0.622$ ($n = 587$)	$r = 0.771$ ($n = 212$)					

$x = p < 0.05$, $xx = p < 0.01$, $xxx = p < 0.001$

After logarithmic conversion of one or both of the variables the correlation was not quite so good ($r(861) = 0.650$, $p < 0.001$). The non-logarithmic relationship between these variables was therefore studied.

In individual testing, all 10 subjects showed a significant relationship between A_1 and A_2 (Table III). At repeated testing the variability between successive test results was minimal. The mean value of the correlation coefficient was much the same and no significant variations were observed in the response pattern ($\chi^2(3) = 0.494$, $p = \text{n.s.}$).

DISCUSSION

The vestibular system can be regarded as a high pass filter which perceives head velocity and causes a compensatory eye deviation to allow unblurred fixation. The velocity signal in the vestibulo-ocular reflex (VOR) arch is processed as in an open loop system (Buizza & Schmid, 1982). Consequently, the system is sensitive to variations in the environment and additional control mechanisms are necessary.

If the vestibular responses are studied in the dark, as in the present study, the determinant of the position of the eyes, i.e. the end-point of the slow phase of nystagmus, must be derived outside the visual resetting system. If the latter were to depend on the proprioceptive signal of the extraocular eye muscle (Fuchs & Kornhuber, 1969), then we would expect a highly synchronous velocity response pattern to be related to the amplitude of nystagmus. However, no such synchrony was found between the amplitude and the velocity of the slow phase of the nystagmus. Our findings therefore support the observations of Keller & Robinson (1971) that there is no functional stretch reflex in the VOR which determines the end-point of the slow phase of nystagmus.

Nevertheless the velocity signal can be employed to determine the end-point of nystagmus, as the integration of velocity over time determines the position of the eyes. Measurement during optokinetic nystagmus indicates that the major variable determining the end-point of nystagmus is, in fact, the eye velocity (Lau et al., 1978). In the present study we also found a close correlation between velocity and displacement of the eyes, thus confirming the close relationship between these two variables. Therefore, the velocity signal might well be the primary source of information whence the amplitude of the slow phase of nystagmus is derived.

There is no direct evidence that the positional signal is processed in the vestibular nuclei or elsewhere in the VOR. Nevertheless, the neurons in the vestibular nuclei are modulated by positional data (Fuchs & Kimm, 1975; Jaeger et al., 1981). Since a lesion in the paramedian pontine reticular formation (PPRF) causes reduced activity of the positional neurons in the vestibular nuclei (Jaeger et al., 1981), it is probable that the positional information in the vestibular nuclei is secondary to that of PPRF (Kaneko et al., 1981). The most likely integrator of positional data would be PPRF in which neurons respond to velocity and positional data of both the slow and fast phase of nystagmus (Keller, 1974; Kaneko et al., 1981). Moreover, a lesion in PPRF causes loss of fast phases (Jaeger et al., 1981). Hence the neural circuitry in PPRF is able to integrate the velocity signal and to keep track of the amplitude and duration of the slow phase of nystagmus.

Our results indicate that the variation in amplitude of the nystagmus slow phase could explain only 35% of the variance of the velocity of the slow phase. Interestingly, the duration of the slow phase of nystagmus is significantly correlated with the velocity of the slow phase. Thus, we presume that also duration of the slow phase is of importance in determining the end-point of nystagmus.

Conceivably a corollary discharge model of eye movement control during the postrotatory nystagmus may be applied. Such a model has been proposed to operate during voluntary eye movements (Henn et al., 1980). The present results seem to confirm the concept that the vestibular nystagmus in the dark may be controlled by two corollary circuits: the "duration circuitry" which should determine the end-point of nystagmus when eye velocity is high, and the "displacement circuitry" active when the eye velocity is low. This dualistic arrangement seems to be feasible in order to prevent excessive blurring of vision. Such blurring might occur if no time locking mechanisms were provided at high nystagmus velocities.

According to Donaghy (1980) the maximum number of fast phases in the cat is four per second. This corresponds well to the intersaccadic interval observed in man when faced with unpredictable step changes in target position (Westheimer, 1954). In such situations, timing would seem to be the predominant regulating factor. The situation appears opposite during low velocity nystagmus when there is sufficient time for fixation. In such conditions amplitude information may become the regulating factor.

The anatomical site of the governing mechanisms deciding when temporal vis-à-vis positional information is to control the nystagmus beat is not known. A lesion in the cerebellum changes both the amplitude and the duration of nystagmus (Collewijn, 1970) and causes mismatching between the amplitudes of the slow and fast phases (Honrubia et al., 1980). Furthermore, the information delivered to the cerebellum precedes the fast phases of nystagmus (Pyykkö et al., 1983). It was proposed that the cerebellum has a function similar to a calibrator for the vestibulo-ocular system (Stark, 1982); the corollary discharges are compared with respect to time and amplitude for the normal range of movement patterns and updated if erroneous. Hence, the cerebellum might be capable to supervise the end-point of nystagmus.

The relationship between amplitudes of slow and fast phase of nystagmus was relatively constant among the subjects. It was, in fact, the only variable which did not show any individual response pattern. Physiologically, the circuitry determining the amplitude of the fast and of the slow phase of nystagmus might be the same. The variation between these two amplitudes may reflect merely the interaction of the durational signal on the positional signal of the slow phase. Even though abla-

tion (Collewyn, 1970) and stimulation (Wolfe, 1969) studies support this concept, single unit recording in awake animals has not yet confirmed this hypothesis (Keller, 1974; Kaneko et al., 1981).

CONCLUSIONS

Since eye velocity signal processed in the VOR operates as an open loop system (Buizza & Schmid, 1982) and is susceptible to error, additional mechanisms are necessary to control the velocity signal. According to the present results it is proposed that two neural circuits may be involved in this function: one "durational circuitry" which calculates time during the slow phase and one "displacement circuitry" which determines the excursion of the eye during the slow phase. Since no relationship was found in the linear regression analysis between temporal and positional data, we assume that both duration and amplitude control of nystagmus are determined independently from each other. Supposingly the time circuitry is more dominant during high nystagmus velocities, allowing sufficient time for fixation. The intrabeat relationship between the amplitudes of slow versus fast phase of nystagmus was not very closely interrelated, indicating that the neural mechanisms governing the fast phase of nystagmus are not particularly accurate in darkness.

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INTRABEAT RELATIONSHIP OF POSTROTATORY NYSTAGMUS IN PATIENTS
WITH NEUROLOGICAL DISORDERS

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ABSTRACT

The intrabeat relationships between velocity, amplitude and duration of the slow phase of nystagmus as well as between amplitudes of slow vs. fast phase of nystagmus were analysed during a postrotatory nystagmus response by using linear regression analysis. Three groups of patients were studied, each consisting of 10 subjects with lesions either in the peripheral vestibular system, in the frontal lobe, or in the brain stem. Irrespective of the site of the lesion, all groups exhibited the same response pattern: a reduction in amplitude control of the end-point of nystagmus and an increase in durational control. The most prominent changes were observed in patients with brain-stem lesion in whom the durational control of the slow phase of nystagmus was constant, with a mean slow phase duration of 150 to 250 ms in the case of 3 to 4 fast phases per second. No alterations were observed in the relationship between amplitude of slow vis-à-vis fast phase. The results indicate that analysis of intrabeat relationship may provide additional data on the site of the disorder affecting the vestibular system.

INTRODUCTION

Numerous attempts have been made to elicit the characteristic differences of nystagmus which would distinguish a disabled subject from a healthy subject, and a subject with a peripheral lesion from a subject with a central lesion (cf. Baloh & Honrubia, 1979). Since variations in nystagmic rhythm are easy to detect, various types of disturbance have been tried in order to correspond to the underlying pathology. In caloric nystagmus, however, Clément (1970), indicated that a variety of rhythm disturbances may occur in a normal subject and that these deviations are merely due to changes in the degree of attentiveness.

Attempts to study internal relationship between the different variables of nystagmus have been made only recently. Buizza et al. (1978) and Schmid (1982) have employed the ratio between the duration of each pair of successive nystagmus beats and the ratio between the amplitudes of each pair of successive fast components. One or both of the so-called interbeat relationships could be pathological and, therefore, characterize the underlying lesion in the vestibular system. So far, clinical applications of this method have been limited to case reports. Pyykkö & Dahlen (1983) have employed linear regression analysis to study the relationship between velocity, amplitude and duration of nystagmus in normal subjects. Their analysis indicated that two basically different strategies are employed in the postrotatory responses, namely, the end-point of nystagmic slow phase may be controlled by "durational" or by "displacement curcuitries" and that the control mechanisms vary depending on the eye velocity.

The purpose of the present work was to extend the study of the intrabeat relationship of nystagmus to include patients with lesions in different parts of the vestibular system. Three groups of patients were examined in the present study: one with a peripheral vestibular lesion, one with a brain-stem lesion and one with a lesion in the frontal lobe. The responses were compared with results in 10 normal subjects.

MATERIAL AND METHODS

Subjects

Ten normal subjects, aged 21 to 62 (mean 41.4 years) were recruited for the determination of normal values (Pyykkö & Dahlen, 1983). They all appeared healthy, with a normal neuro-otological finding and free from any disorder that might interfere with the performance during the test.

Thirty patients with various neurological diseases were selected for this study. They were divided into 3 groups depending on the site of the lesion.

Group 1. Ten patients with a peripheral vestibular lesion. Eight of the patients had vestibular neuronitis, one suffered from acute labyrinth dysfunction and one from Ménière's disease. The mean age of the subjects was 52.9 years (range 35-69 years).

Group 2. Ten patients with lesion in the frontal lobe indicated by speech dyspraxia (Darley et al., 1975). Such disorder denotes a lesion in Broca's speech area, located in the vicinity of the left frontal eye field. Six of the patients had cerebral infarctions, one had been injured in a traffic accident and 3 had a degenerative disease. The mean age of the patients was 56.3 years (range 25-73 years).

Group 3. Ten patients with brain-stem lesion; 6 of them suffered from infarctions of the brain stem, 3 had ischemia of the brain stem, while one had pontine glioma. The mean age of the patients was 63.6 years (range 45-76 years).

Methods

DC electro-oculograms of horizontal and vertical eye movements were recorded simultaneously with an ink-jet recorder (Mingograph M 81, Siemens Elema, Stockholm, Sweden). A 15-Hz filter was used and the paper was fed at 100 mm/s. The accuracy of the interpretation was allowed 1° for amplitude and 10 msec for time events.

The rotatory test was carried out by accelerating the subject in the dark to a constant velocity of 120°/s within 1 sec. After 60 sec the chair was brought to a standstill within 1 sec and the postrotatory response to both clockwise and counterclockwise rotation was measured. The analysis, however, was limited to postrotatory response.

The velocity, amplitude and duration of the slow and fast phases of nystagmus were calculated by manual scoring. By using an interactive computer program, the relationship between these variables was studied on orthogonal scales where the variables

could be plotted on X and Y scales in either a logarithmic or a non-logarithmic mode. A linear regression analysis was performed for the postrotatory responses of each subject. From the analysis the following parameters were derived: intercept (intersection of the regression line with Y-axis), regression coefficient (slope of the regression line), correlation coefficient and standard error of regression.

Statistics

The statistical significance of the correlation coefficient (Edwards, 1979) was examined with Student's t-test. The differences in intercept, regression coefficient and residual errors were evaluated with the Kruskal-Wallis rank test (Siegel, 1956). The differences were considered statistically significant when $p < 0.05$.

Table I. Individual correlation coefficients describing the relationship between amplitude and velocity of slow phase of nystagmus in normal subjects and three groups of patients. Number of observations are given in parentheses.

Group	Subject	1	2	3	4	5	6	7	8	9	10
Normal		***	***	*	***	***	***	***	***	***	***
		r=0.613 (n = 50)	r=0.577 (n = 92)	r=0.185 (n = 99)	r=0.819 (n = 153)	r=0.625 (n = 50)	r=0.599 (n = 41)	r = 0.784 (n = 149)	r=0.256 (n = 121)	r=0.383 (n = 76)	r=0.837 (n = 30)
Vest. periph.		***	***	***	***	***	**	***	***	***	***
		r=0.611 (n = 56)	r=0.774 (n = 57)	r=0.855 (n = 40)	r=0.600 (n = 48)	r=0.555 (n = 63)	r=0.583 (n = 17)	r=0.872 (n = 23)	r=0.451 (n = 73)	r=0.456 (n=58)	r=0.823 (n = 60)
Frontal lobe		***	***	***	***	***	***	*	*	***	*
		r=0.615 (n = 50)	r=0.724 (n = 53)	r=0.764 (n = 84)	r=0.688 (n = 44)	r=0.594 (n = 64)	r=0.886 (n = 44)	r=0.446 (n = 18)	r=-0.136 (n = 13)	r=0.614 (n=30)	r=0.237 (n=59)
Brain stem		***	***	***	***	***	***	***	***	***	***
		r=0.630 (n = 50)	r=0.659 (n = 37)	r= 0.910 (n = 31)	r=0.471 (n = 65)	r=0.794 (n = 31)	r=0.724 (n = 66)	r=0.404 (n = 80)	r=0.722 (n = 108)	r=0.654 (n = 78)	r=0.870 (n = 49)

* p<0.05
 ** p<0.01
 *** p<0.001

RESULTS

1. Relationship between velocity (V_1) and amplitude (A_1) of slow phase of nystagmus

Fig. 1 shows the mean slow-phase velocity (V_1) at a given amplitude (A_1) of the slow phase of nystagmus in normal subjects and in the three groups of patients. Linear regression lines are also drawn. The relationship between

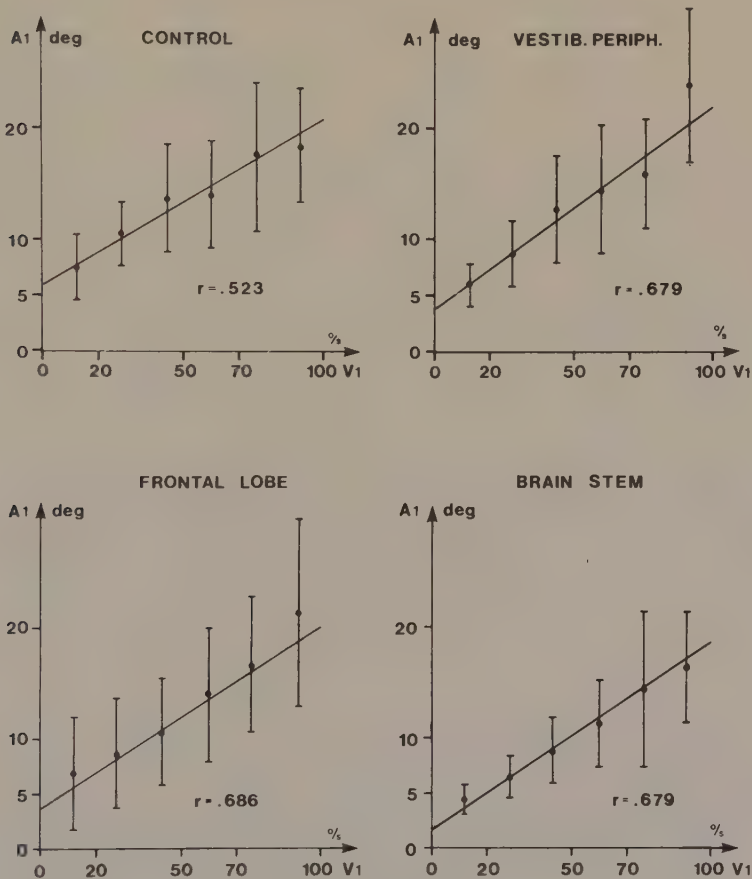


Fig. 1. Intrabeat relationship between velocity (V_1) and amplitude (A_1) of the slow phase of nystagmus in normal subjects, in patients with vestibular lesions, in patients with frontal lobe lesions and in patients with brain-stem lesions. Mean values and standard deviations for given velocity classes are shown, as well as linear regression lines with correlation coefficients.

these variables in the groups with disorders in the peripheral vestibular system ($r(495) = 0.679$, $p < 0.001$), brain stem ($r(595) = 0.679$, $p < 0.001$) and frontal lobe ($r(469) = 0.686$, $p < 0.001$) exhibited a rather closer correlation than that found in the normal group ($r(861) = 0.523$, $p < 0.001$), though the differences were not statistically significant. In individual responses, all but one patient exhibited a statistically significant correlation between A_1 and V_1 (Table I).

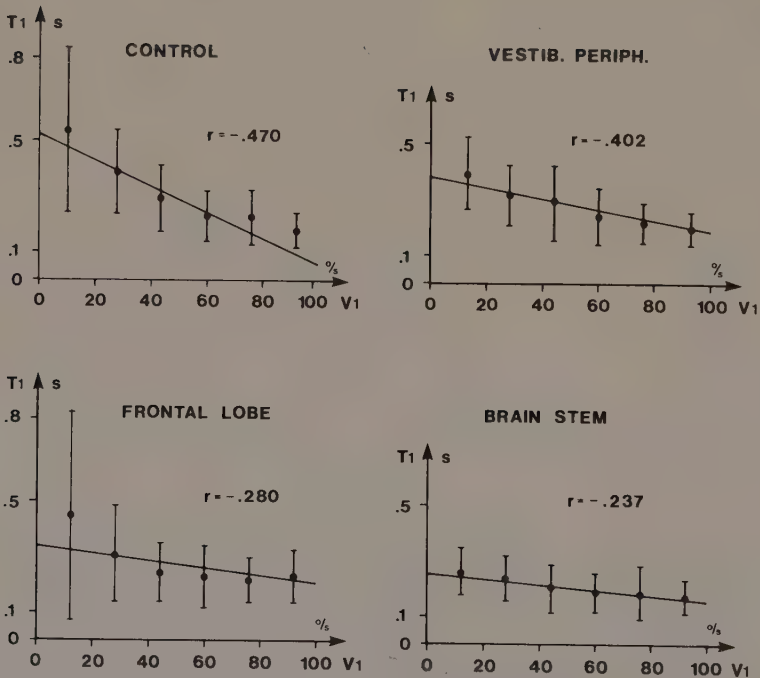


Fig. 2. Intrabeat relationship between velocity (V_1) and duration (T_1) of the slow phase of nystagmus. For subjects and measures, see Fig. 1.

Consistent with the results of correlation coefficients, the slope of the regression line was, in general, steeper in patients than in normal subjects, but no statistically significant differences were observed between the groups. Furthermore, the standard error of regression did not differ between the groups, indicating the same degree of variability in beat-to-beat relationship between the groups.

Patients with brain-stem disorders, however, exhibited lower intercept values than did control subjects ($H(1) = 4.64$, $p < 0.05$). In other groups, no statistically significant differences in the intercept could be discerned.

2. Relationship between velocity (V_1) and duration (T_1) of slow phase of nystagmus

Fig. 2 displays the mean values of the duration (T_1) at a given velocity (V_1) of slow phase of nystagmus in normal subjects and in the three groups of patients. Regression lines are shown in the same figure. In all groups the relationship between T_1 and V_1 based on group data was statistically highly significant ($p < 0.001$). However, the extent of correlation between T_1 and V_1 varied between different groups ($H(3) = 7.13$, $p < 0.05$). The correlation was best in normal subjects and poorest in patients with brain-stem disorder. Individual correlation coefficients are shown in Table II.

Consistently, also as regards regression coefficient, we observed significant differences between the four groups ($H(3) = 14.55$, $p < 0.01$). In a pairwise comparison, significant differences were discerned between normal subjects and the following groups: patients with vestibular neuronitis ($H(1) = 4.97$, $p < 0.05$), patients with frontal lobe lesion ($H(1) = 4.64$, $p < 0.01$) and patients with brain-stem lesion ($H(1) = 10.49$, $p < 0.001$). Moreover, we found that patients with brain-stem lesion differed from those with vestibular neuronitis by exhibiting lower regression coefficients ($H(1) = 5.316$, $p < 0.05$).

Regarding intercepts, significant differences could be discerned between normal subjects and patients with frontal lobe lesion ($H(1) = 6.23$, $p < 0.05$) and patients with brain-stem lesion ($H(1) = 14.00$, $p < 0.001$). Only a tendency to a reduced intercept was observed in patients with peripheral vestibular disorder. Nevertheless, differences between patients with a peripheral vestibular lesion and those with brain-stem lesion were statistically significant ($H(1) = 8.04$, $p < 0.01$).

Table II. Individual correlation coefficients describing the relationship between duration and velocity of slow phase of nystagmus in normal subjects and three groups of patients. Number of observations are given in parenthesis.

Group	Subject	1	2	3	4	5	6	7	8	9	10
Normal	$r = -0.288$ (n = 50)	*** $r = -0.502$ (n = 92)	*** $r = -0.774$ (n = 99)	*** $r = -0.415$ (n = 153)	*** $r = -0.415$ (n = 153)	** $r = -0.359$ (n = 50)	*** $r = -0.600$ (n = 41)	*** $r = -0.693$ (n = 149)	*** $r = -0.660$ (n = 121)	*** $r = -0.513$ (n = 76)	* $r = -0.358$ (n = 30)
Vestib. periph.	$r = -0.723$ (n = 56)	*** $r = -0.699$ (n = 57)	** $r = -0.433$ (n = 40)	*** $r = -0.480$ (n = 48)	*** $r = -0.480$ (n = 48)	** $r = -0.353$ (n = 63)	*** $r = -0.730$ (n = 17)	*** $r = -0.824$ (n = 23)	* $r = -0.390$ (n = 32)	*** $r = -0.623$ (n = 38)	*** $r = -0.620$ (n = 60)
Frontal lobe	$r = -0.370$ (n = 50)	** $r = -0.325$ (n = 53)	*** $r = -0.445$ (n = 84)	*** $r = -0.157$ (n = 44)	*** $r = -0.157$ (n = 44)	** $r = -0.370$ (n = 64)	* $r = -0.340$ (n = 44)	*** $r = -0.205$ (n = 18)	** $r = -0.690$ (n = 13)	*** $r = -0.568$ (n = 30)	*** $r = -0.404$ (n = 69)
Brain stem	$r = -0.441$ (n = 50)	*** $r = -0.126$ (n = 37)	* $r = -0.382$ (n = 31)	*** $r = -0.523$ (n = 65)	*** $r = -0.523$ (n = 65)	*** $r = -0.027$ (n = 31)	*** $r = -0.620$ (n = 66)	*** $r = -0.709$ (n = 80)	*** $r = -0.603$ (n = 108)	*** $r = -0.401$ (n = 78)	*** $r = -0.082$ (n = 49)

* $p < 0.05$
 ** $p < 0.01$
 *** $p < 0.001$

Table III. Individual correlation coefficients describing the relationship between amplitude of slow respective fast phases of nystagmus in normal subjects and three groups of patients. Number of observations are given in parenthesis.

Group	Subject	1	2	3	4	5	6	7	8	9	10
Normal		*** r=0.487 (n = 50)	*** r=0.660 (n = 92)	*** r=0.582 (n = 99)	*** r=0.784 (n = 153)	*** r=0.708 (n = 50)	* r=0.333 (n = 41)	*** r=0.516 (n = 149)	*** r=0.454 (n = 121)	*** r=0.417 (n = 76)	*** r=0.712 (n = 30)
Vest. periph.		*** r=0.527 (n = 56)	*** r=0.494 (n = 57)	*** r=0.505 (n = 40)	*** r=0.653 (n = 48)	** r=0.312 (n = 63)	* r=0.182 (n = 17)	* r=0.422 (n = 23)	* r=0.210 (n = 73)	* r=0.225 (n = 58)	*** r=0.686 (n = 60)
Frontal lobe		*** r=0.592 (n = 50)	*** r=0.631 (n = 53)	*** r=0.759 (n = 84)	*** r=0.692 (n = 44)	*** r=0.609 (n = 64)	* r=0.252 (n = 44)	*** r=0.774 (n = 18)	*** r=0.312 (n = 13)	*** r=0.248 (n = 30)	*** r=0.426 (n = 69)
Brain stem		*** r=0.459 (n = 50)	*** r=0.710 (n = 37)	*** r=0.645 (n = 31)	*** r=0.397 (n = 65)	* r=0.402 (n = 31)	*** r=0.682 (n = 66)	*** r=0.635 (n = 80)	*** r=0.551 (n = 108)	*** r=0.448 (n = 78)	*** r=0.602 (n = 49)

*

p<0.05

**

p<0.01

p<0.001

3. Relationship between amplitude of slow phase (A_1) and of fast phase (A_2) of nystagmus

In all groups of patients the relationship between A_1 and A_2 was highly significant ($p < 0.001$) (Fig. 3). No differences could be discerned between individual correlation coefficients (Table III), however. No significant differences were observed regarding regression coefficients, between normal subjects and the different groups of patients. Nor could any differences be demonstrated either in the intercept or in the error of regression between normal subjects and the groups of patients.

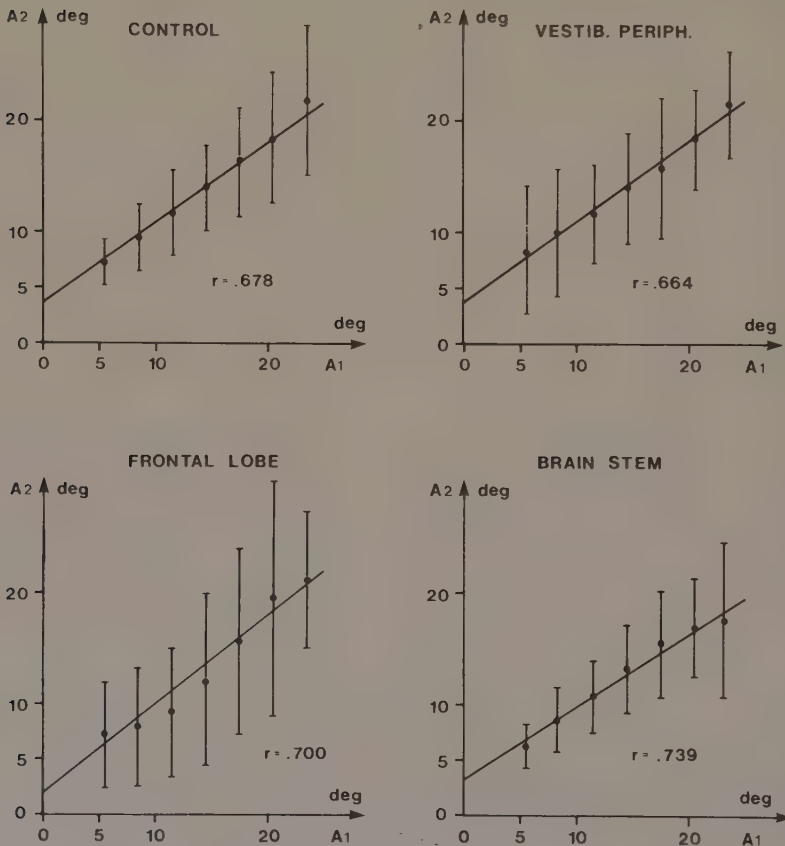


Fig. 3. Intrabeat relationship between amplitude of slow phase (A_1) and amplitude of fast phase (A_2) of nystagmus. For subjects and measures, see Fig. 1.

DISCUSSION

In the present study the relationship between different components of nystagmus was examined on the basis of beat by beat analysis of postrotatory reaction test by using linear regression analysis. The responses in patients with a peripheral vestibular lesion, with a frontal lobe lesion and with a brain-stem lesion were compared with results from normal subjects. Typically, the control of end-point of nystagmus exerted by amplitude information was impaired in the different groups of patients and the duration of the slow phase was used in exerting control to a greater degree than in normal subjects. This finding was especially pronounced in patients with a brain-stem lesion in whom the duration of slow phase became fixed to allow greater security for the nystagmus. In the relationship between the amplitude of slow vs. fast phase of nystagmus, no differences were observed between any of the groups studied.

1. Enhancement of time control of nystagmus after lesion of vestibular system

In the present study the tests were conducted in total darkness. The signal of the position of the eyes must in such conditions be derived from outside the visual resetting mechanisms. Since there is no evidence of a functioning stretch reflex of the extraocular muscles in primates (Keller & Robinson, 1971), it seems likely that the positional signal is extracted from the velocity signal at the site of the brain stem (Jaeger et al., 1981; Buizza & Schmid, 1982; Nakao et al., 1982; Pyykkö & Dahlen, 1983).

The relationship between A_1 and V_1 showed a tendency to become closer in lesions affecting the vestibular system. Such a close linkage indicates an increased automation in the amplitude resetting mechanisms. Consistently, when the vestibular system or mechanisms controlling it are lesioned, time control over the nystagmus becomes more important than the amplitude control mechanisms. However, there was still a tendency for differences among the various groups of patients. Patients with a vestibular lesion were least affected, and patients with brain-stem disorder were most affected. It was remarkable that in the patients with a brain-stem lesion the duration of nystagmus slow phase seemed to be temporally fixed, the mean duration of this was varying between 0.15 and 0.25 s. This duration applies to the occurrence of fast phases with frequency of 3 to 4 Hz. According to Donaghy (1980) 4 Hz seems to be the maximum number of fast phases still ensuring unblurred fixation during the slow phase.

The patients with a brain-stem lesion responded with lower nystagmus amplitudes to a given velocity than did normal subjects. Since the regression coefficient did not differ between these groups, the lower intercept value in the brain-

-stem group indicates that in the generation of the same nystagmus amplitude as in the normal subjects, a higher velocity in the slow phase is needed. This elevated threshold for amplitude release seems to be a contributing factor to the petit ecriture type of nystagmus met with in patients with brain-stem lesions (Jung & Kornhuber, 1964).

2. Site of lesion in vestibular system as a determinant of intrabeat relationship

The reason why the various types of lesions caused a rather stereotype disorder in the vestibular responses may be explained by the basic need for great stability in the vestibulo-ocular reflex. Such stability is secured in various ways. In patients with an acute peripheral vestibular lesion the difference in the influx from the labyrinths provides conflicting information. Consequently, neurons in the vestibular system are facilitated to a different extent by the two labyrinths (Nakao et al., 1982). Thus, positional information derived from the labyrinthine influx will provide erroneous data. The "duration circuitry" should therefore become more dominant in governing ocular excursion during the slow phase of nystagmus, as was also confirmed by the data in the present study.

The frontal lobe is a site of the neuronal population initiating voluntary eye movements (Goldberg & Bushnell, 1981) as well as controlling nystagmus and eye-head coordination (Bizzi, 1968; Bizzi & Schiller, 1970). As a result of a lesion affecting this brain structure predictability of the eye movements will be reduced (Pyykkö et al., 1983). In the context of reflexive eye movements, the lack of supratentorial control mechanisms may actually lead to unpredictable changes in nystagmus, e.g. absence of beats and hyperreflexia (Dahlen et al., 1983). Since the control of the velocity will be impaired, it also follows that the amplitude control on the end-point of slow phase of nystagmus will become unpredictable. Consequently, temporal control of nystagmus should be enhanced, as was observed in the results.

In lesions affecting the brain stem where, it is assumed, the positional data is derived from the velocity data, the risk of miscalculation exists. Consequently, "durational circuitry" becomes more dominant, but since the fault is in the "immediate motor programmer" for the nystagmus (Raphan & Cohen, 1978), the "durational circuitry" may also become faulty. By fixing the duration of the slow phase of nystagmus the error may be minimized and the shape of the nystagmus will accord with the well-known petit ecriture.

CONCLUSIONS

The intrabéat analysis of nystagmus in patients with defined lesions may allow to understand some compensatory mechanisms of the brain due to a dysfunction of the control system. According to the results the reaction mode of vestibular responses in the dark becomes rather stereotype, not because of the type of lesion but because of switching to more secure and basic control mechanisms of nystagmus.

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DYSPRAXIA OF SPEECH AND OF EYE MOTILITY

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Abstract. Five patients with a disturbance of their preprogramming of speech (dyspraxia of speech) were exposed to a comprehensive eye-motor test-battery. The saccades were found hypometric and inaccurate with irregular intervening pauses. The finding was interpreted as due to an extension of lesions from frontal cortical speech areas into visual motor cortex disturbing the normal preprogramming of voluntary saccades. The results were interpreted as supporting the assumption that voluntary saccades are initiated in the frontal cortex. An increase of vestibular nystagmus in these cases was related to a release of vestibular nystagmus due to the disappearance of cortical inhibition on brain stem activity.

This paper will deal with disturbances in the same patients of two seemingly unrelated voluntary activities, that of preprogramming of speech and that of preprogramming of voluntary fast eye movements, the voluntary saccades. Both types of activities demand the will of the patient as well as a large amount of coordination of muscle activity and both activities may be triggered in the frontal cortex in front of the pre-central gyrus.

This specific disturbance of programming of speech may be due to a lesion in the frontal cortex resulting in a typical speech pattern (Darley et al., 1975). In these cases, although the persons are capable of finding the right word from their "bank of words", they are unable to initiate a proper combination of muscle activity to produce the word. Instead they will produce, with a normal tone and articulation and normal strength, faulty constructions of that word. They are aware of their mistakes and will repeatedly try to

correct themselves frequently without success.

This disturbance of speech has been called apraxia (Liepman, 1914; Darley et al., 1975). Since this term would indicate a complete inability to control speech, which rarely is the case, we have suggested for this disturbance and have in this paper used the term dyspraxia.

In these patients a pronounced decrease of accuracy of fast eye movements was frequently found. These patients seem to have lost their normal ability to preprogram voluntary eye movements together with their ability to preprogram speech. This combination initiated the present study of various types of eye movements in patients in whom the dyspraxia of speech indicated a frontal cortical lesion.

MATERIAL AND METHODS

Five patients with a speech disorder of the dyspractic type were examined and compared with five age-matched normal subjects (Table I). The speech disorder was classified according to conventional phoniatric tests (Johns & Darley, 1970). Great care was taken to exclude patients with impressive or expressive aphasia from the study. However, in all patients with dyspraxia a component of expressive aphasia could be detected. This usually was of a minor degree when compared with the disorder caused by motor dyspraxia.

Table I. Data on five patients having dyspraxia

Patient	Age (years)	Symptoms and findings apart from dyspraxia	Diagnosis	Duration of speech disorders
1 (A. S.)	67	Asymptomatic hypertension + extrapyramidal components	Multifocal.	2 years
2 (S.-E. S.)	57	Inability to voluntarily activate cranial nerves	Vasc. deg. of CNS	2 years
3 (B. K.)	37	Right sided hemiparesis	Multifocal degeneration process in CNS, ALS?	1 month
4 (R. E.)	68	Difficulties in memory	Left-sided anterolateral cerebral infarction	6 months
5 (N. J.)	24	Right sided hemiparesis	Presenile dementia	2 months
			Subarachnoidal bleeding, aneurysm	

Conventional electronystagmographic equipment (Henriksson et al., 1967; Henriksson et al., 1972) was used. The methods, in brief, were as follows; Horizontal eye movements were recorded binocularly and vertical eye movements from each eye separately with a 4-channel DC-coupled pen-recorded (Mino-graph 81, Siemens-Elema, Stockholm, Sweden) with an upper cut-off frequency of 15 Hz and an infinite time constant; commercial electrodes (Medicotest®) with jelly were used. The subjects were examined with the respect to:

1. Command eye movements of 20°.
2. Pursuit eye movements with a constant target velocity of 20° s⁻¹ and with a pendular target.
3. Optokinetic nystagmus in a wholefield optokinetic drum, accelerating from a velocity of 0° to 60° s⁻¹ in 15 s.
4. Vestibular nystagmus was studied with open eyes in darkness (a) induced by caloric stimulation with water of 30°C and 44°C for 20² and (b) induced by angular accelerations of 120° s⁻² for 1 s.

RESULTS

1. Command eye movements

The voluntary saccades were examined and compared with those of the normals (Fig. 1) with respect to the following parameters:

A. *Accuracy.* In four of the five patients there was a pronounced undershoot of the

command eye movements which were each performed as two to four smaller saccades. In one of the patients (No. 4) there were also overshoots by the eyes passing the target by five to eight degrees.

B. *Fixation periods.* The time intervals between the initiation of saccades of different directions were also studied. In four of the five patients these periods were very irregular while in one case (no. 2) these periods were significantly prolonged.

C. *Velocity of saccades.* The velocity of the saccades was also examined but did not show any differences from the normal subjects.

2. Following eye movements

Following eye movements were normal in patients 2 and 5 and a slight disturbance was seen in patient 1. Gross abnormalities with irregular disruptions of the smooth eye movements by saccades were found in patients 3 and 4 (Fig. 2). Four of the normal subjects presented completely smooth eye movements, while one of these subjects showed a slight irregularity in his tracking pattern.

3. Optokinetic eye movements

The optokinetic nystagmus was within normal limits in all patients (Fig. 3). The fast and slow phases were consistently regular in both directions. The amplitudes were, however, smaller and the frequency higher in

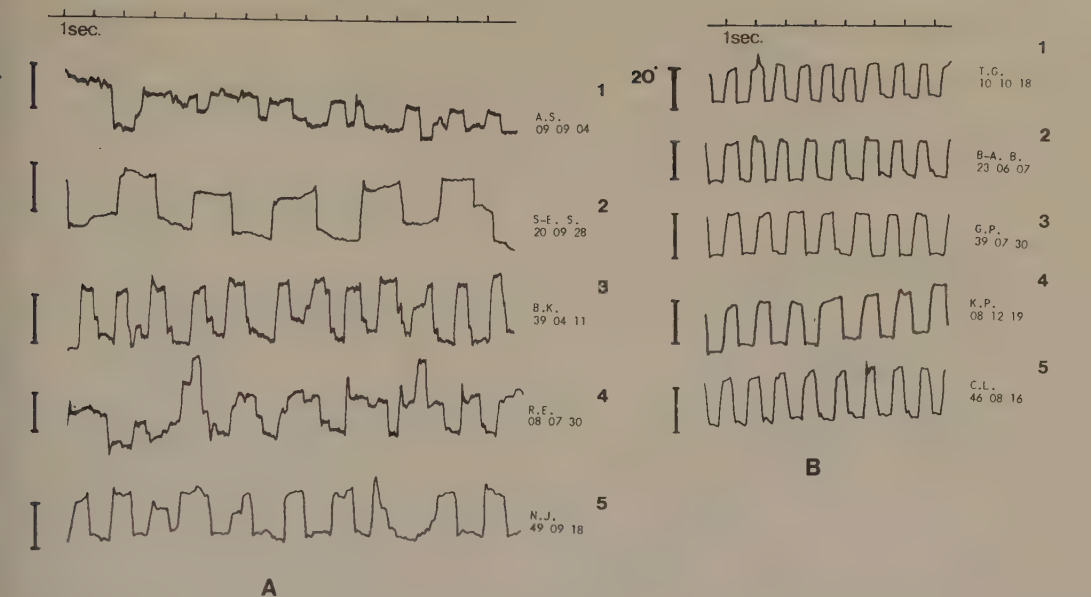


Fig. 1. The command eye movements of 20°; (A) in patients with dyspraxia; (B) in healthy controls. The

time scale is shown in the uppermost curve in both pictures.

patients 3, 4 and 1. The same patients showed a disturbance of following eye movements. When comparing the optokinetic patterns of normals and of the diseased there were no clear-cut differences. However, the amplitude of optokinetic nystagmus of the patients was slightly larger than that of the normals.

The eye movements in rotation tests

vestibular nystagmus induced by rotation in darkness was normal in all patients except patient 4 in whom the amplitudes were very low. The nystagmus was rhythmic, especially so in patients 1 and 5 (Fig. 4). The average amplitude was larger in the group of patients than in the group of normals.

Eye movements in caloric tests

The nystagmus caused by caloric irrigation of the ears in the dark was remarkably regular and quite symmetrical in all patients (Fig. 5). The amplitudes of the normals were significantly smaller than those of the patients. The nystagmus of remarkably high amplitude was found with in patients 1, 3 and 4. These

patients showed a disturbance of the following movements and a lower amplitude of optokinetic nystagmus than the two remaining patients.

In an effort to evaluate the correlation between the different nystagmus responses and the pursuit ability, four characters were ranked for comparison, the smoothness of the following movements and the amplitudes of caloric, optokinetic and postrotatory nystagmus. In this way the amplitude of caloric and of optokinetic nystagmus could be plotted against smooth tracking ability (Fig. 6). This plotting indicates that caloric amplitudes decrease with increasing tracking ability while optokinetic nystagmus increases with this ability. The postrotatory nystagmus pattern was so similar in four cases that no ranking could be made.

RESULTS

Patients with dyspraxia of speech produce saccades of normal velocity but with pronounced dysmetria and with prolongation of pauses between saccades. In spite of this the

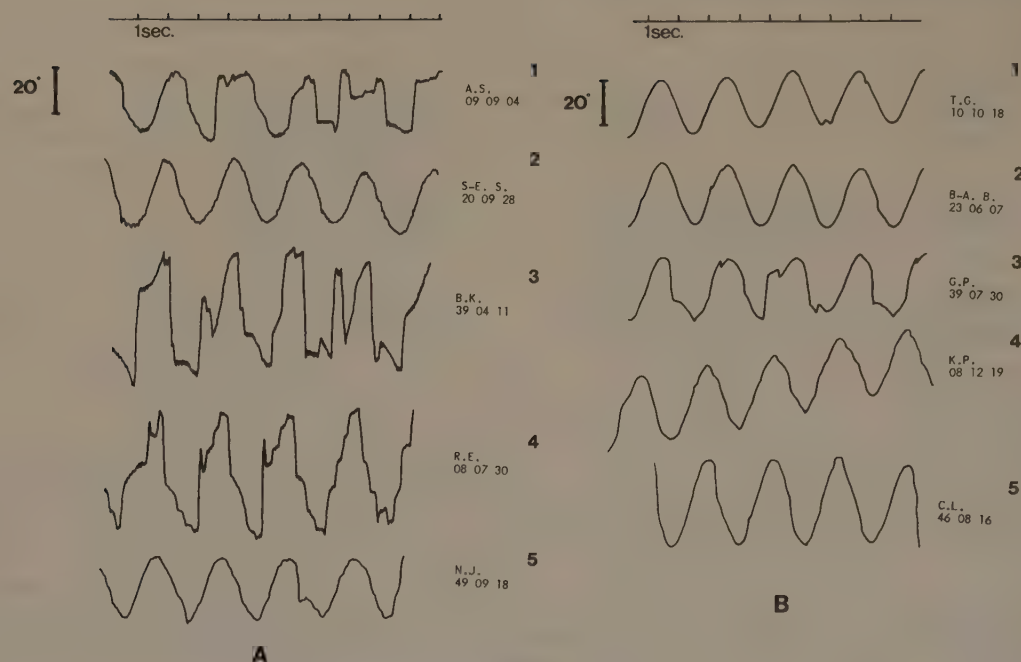


Fig. 2. The following eye movements with a pendular stimulus; (A) patients with dyspraxia; (B) health controls.

postrotatory and the caloric nystagmus were brisk and of larger amplitude than in normals.

Three of the patients showed disturbances in pursuit eye movements. These three patients had a pronounced increase in the amplitude of the caloric nystagmus in relation to the other patients and also when compared to normal subjects.

DISCUSSION

1. A comparison between features of speech of eye movements

The pronounced relationship between speech disorder of the dyspractic type and disturbances in execution of command eye movements has not been previously described.

In the highest centers speech would seem to be processed in three different stages: (a) Development of purpose; (b) integrated planning; and, (c) programming of the execution of speech (Darley et al., 1975).

Pure dyspraxia is defined as a disorder of

the third stage. About fifteen features have been described as typical for dyspraxia (Johns & La Pointe, 1975). At least three such characteristics, accuracy, strength and tempo of speech all seem to have counterparts in voluntary eye movements.

A. Accuracy. The dyspractic patients seem to be unable to accomplish the sequence of sounds which form the word. The word is frequently distorted by inaccurate sounds or syllables. Because the sensorial verbal systems in these patients are intact they will detect their error and try to correct the error with great effort.

This inaccuracy in speech is reflected in the command eye movements by an inability to execute a saccade of appropriate size. The saccade produced will be inaccurate, frequently too small and (as in dyspractic speech) followed by corrections. It will thus be split up, frequently into two or more shorter saccades with or without overshoots.

B. Strength. Strength of dyspractic speech may be normal with the words uttered with

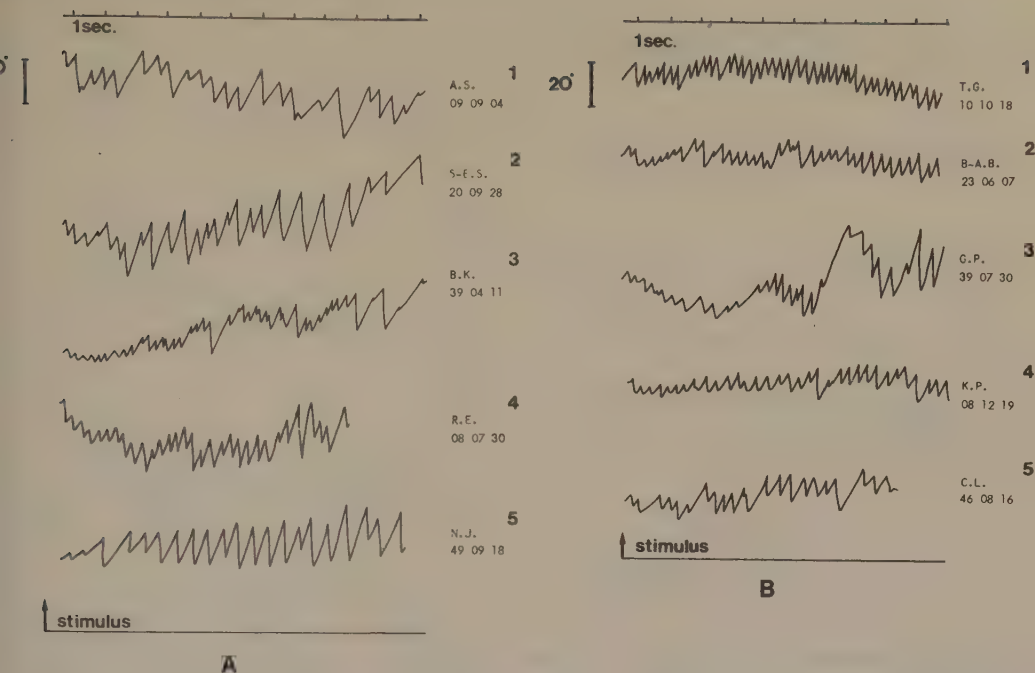


Fig. 3. The optokinetic eye movements; (A) in patients with dyspraxia; (B) in healthy controls.

normal force. The corresponding dimension of the eye movement should be the velocity. The velocities of the disturbed saccades were accordingly found normal in spite of the splitting up into many saccades.

C. Tempo. A certain prolongation between consecutive letters, syllables or words seems typical of the dyspractic speech. The tempo is staccato with long intermissions during which the patient seems to search for the appropriate word or syllable. In eye movements this pattern is reflected by prolongations of or variations in the periods between consecutive saccades.

We may now claim at least that these three features of speech, accuracy, strength and tempo, are reflected in corresponding features in patterns of eye movements.

Location of excitatory neurons for voluntary saccades

Earlier concepts about the role of cortex in initiating eye movements were largely based

on clinical observations (Holmes, 1938; Cogan & Adams, 1953), ablation studies (Latto & Cowey, 1971; Pasik & Pasik, 1964) and observations of eye movements induced by stimulation of the cortex (Ferrier, 1875; Penfield & Boldrey, 1937; Pasik & Pasik, 1964). All these studies indicated that voluntary saccades are probably triggered by area 8 of the frontal cortex. This assumption was further supported by observations that ramp-like positive premotor potentials have been shown in EEG in the frontal and parietal areas (Becker et al., 1968; Barlow & Ciganek, 1969; Kurtzberg & Vaughan, 1973).

Recent experiments with single unit recordings have, however, largely contradicted these concepts. Thus in single unit recordings, Bizzi (1968), Bizzi & Schiller (1970) and Mohler et al. (1973) were not able to detect any presaccadic activity in the prefrontal area, although they could record activity during the saccade as well as during slow eye movements.

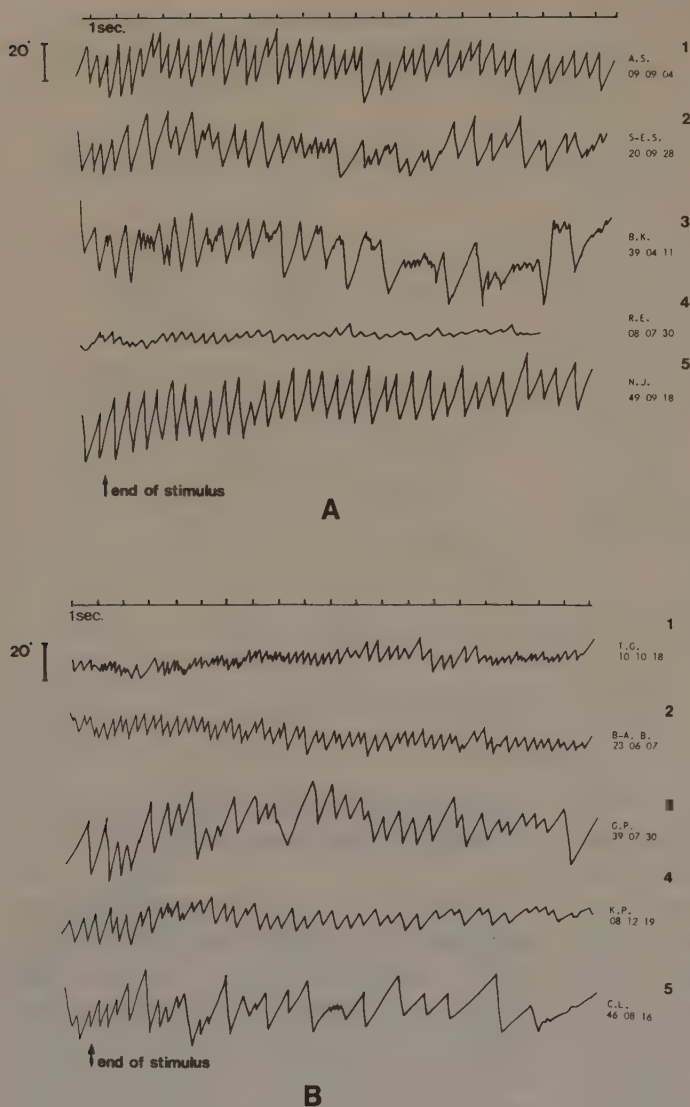


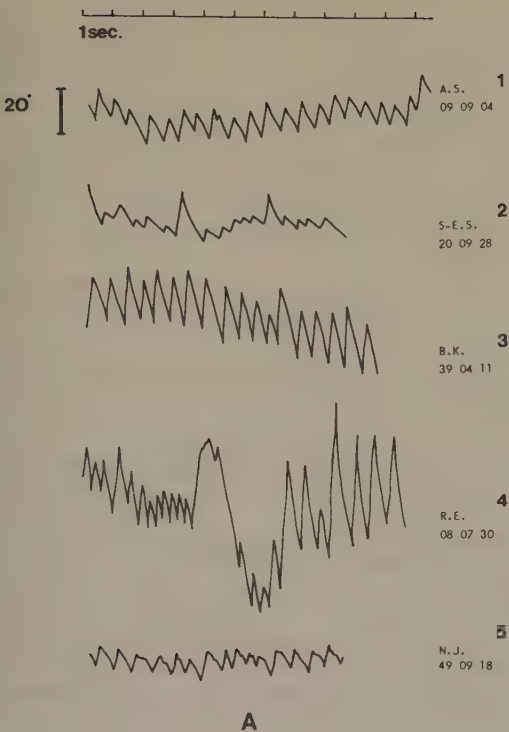
Fig. 4. The eye movements provoked by rotating the subjects with an acceleration of 120° s^{-2} for 1 sec and then at constant velocity; (A) patients with dyspraxia; (B) healthy controls.

Based on such contradictory observations the exact mechanisms by which the voluntary eye movements are triggered and controlled have remained obscure. The present findings do, however, support the idea that command eye movements are initiated in the frontal cortex. We have based this assumption upon the idea that the dyspraxia of speech is due to a frontal cortical lesion which in some cases extend to neighbouring cortical areas responsible for initiation of this type of eye movement.

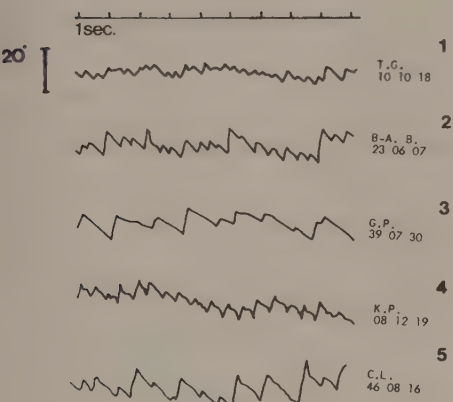
The lack of neuronal activity of the frontal

visual cortex before the voluntary saccade (Bizzi, 1968; Bizzi & Schiller, 1970; Mohler et al., 1973) could be attributed, we presume, to the possibility that no "voluntary" saccades are initiated in the frontal lobe of monkeys. The neurons studied by Bizzi should then have only a control function of saccades initiated elsewhere (Hoyt & Frisén, 1975).

The ability to produce true voluntary eye movements in contrast to such by interest may not yet have been developed in monkeys (as speech) while it is well established



A



B

Fig. 5. Nystagmus recorded after cold water (30°) irrigation of right ear; (A) in patients with dyspraxia; (B) in healthy controls.

in man. It may be suggested that most of the eye movements studied in monkeys in laboratories were initiated by interest and the eye movements thus excited in area 7 (Lynch et al., 1977). The command eye movements in man may be an effect of a

Ranked nystagmus amplitude

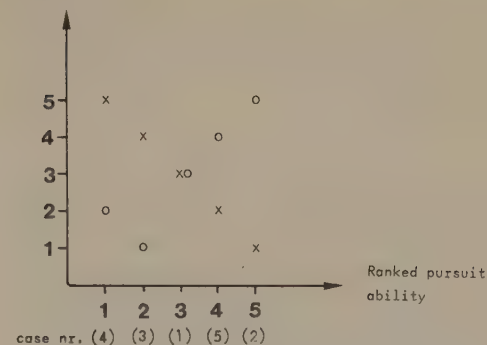


Fig. 6. Ranked amplitude of caloric (x) and of optokinetic (o) nystagmus as a function of pursuit ability.

process in frontal cortex, phylogenetically newly developed speech.

3. Increase of caloric nystagmus amplitude—an effect of reduced cortical inhibition?

An intense and rhythmic caloric nystagmus response was found in all dyspractic subjects. The largest amplitudes were found when disturbances of saccades as well as pursuit eye movements indicated more extensive cortical lesions. The large nystagmus amplitude may thus be an effect of reduction of cortical inhibition of a meaningless vestibular response.

A careful analysis also of properties of the saccades may then be useful for evaluation of the vestibular responses and also helpful for discriminating between patients with aphasia and dyspraxia, which is of interest for the phoniatrist and his selection of treatment.

ZUSAMMENFASSUNG

Fünf Patienten mit Sprechprogrammierungsstörungen (oralen, verbalen Dyspraxie) wurden mit einer umfassenden Serie von Prüfungen der Augenmotorik untersucht. Es ergaben sich hypometrische und ungenaue Saccaden mit unregelmäßigen zwischenliegenden Pausen. Die Befunde deuten auf eine Ausbreitung der corticalen Läsionen vom frontalen Abschnitt für Sprache bis zum motorischen Cortex für Augenmotorik mit daraus resultierenden Störungen der Vorprogrammierung von willkürlichen Saccaden. Diese Resultate bestätigen die

Annahme, daß willkürliche Saccaden in der Rinde des Stirnlappens ausgelöst werden. Eine Vermehrung des vestibulären Nystagmus in den beschriebenen Fällen steht im Zusammenhang mit einer Enthemmung auf Grund eines Wegfalles der cortikalen Inhibition auf die Aktivität des Hirnstammes.

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EYE MOVEMENTS IN PATIENTS WITH SPEECH DYSPRAXIA

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ABSTRACT

Saccades, smooth pursuit and angular acceleration induced nystagmus were analysed quantitatively in 10 patients with speech dyspraxia. The saccades were less accurate, had a prolonged reaction time and showed a tendency to reduced peak velocity, though only contralateral to the lesion. Smooth pursuit was impaired, with a reduction in maximum velocity gain. The vestibular responses tended to be hyperactive, indicating facilitated brain-stem reflexes. The findings show that a lesion in the frontal eye field can produce various oculomotor disturbances, in which the triggering of eye movements and their control, and pacing of the various movement sequences are disturbed. In addition, anticipation of a movement pattern requiring volition may be greatly impaired.

The frontal lobe initiates and controls movements of the body and of the eyes. How this is brought about is not known in detail. The effect of a frontal lobe lesion on body movements may be described by a de-automation of complex and skilled movements (cf. Fuster, 1980). Analysis of these disturbances indicates that such patients have difficulty in initiating one movement and continuing smoothly to the next. This motor disability constitutes a dyspraxia of performance (Geschwind, 1965).

Frontal lobe lesions also disturb eye motor performance. An irritative lesion causes the eyes to deviate towards the opposite side (Holmes, 1938), whereas a destructive process manifests itself by eye movements ("deviation conjuguée") towards the lesion side. Very little interest has, however, been evidenced in the concept of de-automation of complex eye motor movements or the possible activation of elementary automatism as found for other kinds of locomotion. Nevertheless, it was reported in earlier works (Dahlen et al., 1980; Henriksson et al., 1981; Schalén et al., 1982) that subjects with frontal lobe lesions associated with speech dyspraxia would produce a "de-automation" of accurate voluntary saccades.

The aim of the present study was to extend our previous findings on eye motility in patients with speech dyspraxia (Dahlen et al., 1980) and to analyse quantitatively disturbances in saccades, smooth pursuit and in nystagmus induced by angular acceleration.

MATERIAL AND METHODS

Subjects

Ten patients with speech dyspraxia (mean age 56.3 years, range 25-73 years) were studied. Based on neurological findings, seven of the subjects had a predominantly unilateral left frontal lobe lesion. General reflex enhancement was met with in 3 patients and they presumably had bilateral hemispherical lesions. The eye movements were recorded 2 weeks-60 months after onset of the cerebral symptoms. All patients were co-operative. All CNS-influencing medication was discontinued at least 48 hours prior to the investigation. Patients' ages, the duration of neurological symptoms and the diagnoses are set out in Table I.

Table I. *Diagnosis, age, duration of symptoms, and neurological findings in the patients.*

No	Diagnosis	Age	Duration of symptoms	Neurological findings/signs
1	Infarction	48	11 months	Hemiparesis right
2	Infarction	67	3 weeks	Hemiparesis right
3	Infarction	65	2 weeks	Hemiparesis right
4	Infarction	36	2 years	Hemiparesis right
5	Infarction	73	4 months	Hemiparesis right
6	Infarction	59	2 weeks	General stretch-reflex facilitation
7	Contusion	25	2 months	Hemiparesis right
8	Atrophy	55	6 months	Reflex enhancements right
9	Atrophy	68	5 years	General stretch-reflex facilitation
10	Atrophy	67	3 years	General stretch-reflex facilitation

Twenty normal subjects, aged 23 to 72 years, were recruited for the determination of normative values (Henriksson et al., 1980; Schalén, 1980).

Recording of eye movements

Eye movements were recorded with direct current electro-oculography (EOG) technique, using an ink-jet writer (Mingograph M81, Siemens Elema, Stockholm, Sweden) and filter with an upper cut-off frequency of 15 Hz. The paper was fed at a speed of 100 mm/sec during the recording of saccades and nystagmus, whereas during the tracking test the paper velocity was 25 mm/sec. Calibrations of eye movements were made using two pairs of light diodes subtending angles of 20 and 60°. Commercial silver-silver chloride electrodes and jelly were used (Medicotest®). The horizontal eye movements were recorded binocularly and the vertical ones monocularly.

Testing of saccades

The visual targets were light diodes of different colours, mounted on a horizontal bar, placed 120 cm in front of the subject. The pairs of diodes could be switched on-off so that gaze shifts of 5, 10, 20, 30, 40 and 60° would result. The subjects were asked to move their gaze as quickly as possible between each pair of actual diodes. Peak velocity of the saccades was measured by manual scoring. The saccades were classified into six categories, with mean amplitudes of 5, 10, 20, 30, 40 and 60° (Henriksson et al., 1980).

Reaction time for saccades was measured at randomly lighted targets subtending 60° of visual angle. Saccade accuracy was measured as an amplitude of the initial saccade. At least 10 consecutive saccades at each amplitude and direction were measured.

Ability to execute rapid refixational saccades between alternately shifting targets was measured at light-emitting diode targets placed at visual angles of 20 and 60°. The target shifted between the two positions at time events of 1.2, 1.0, 0.8, 0.6, and 0.4 sec intervals. For a normal response, five correctly spaced saccades at each amplitude and time interval were required.

Testing of tracking eye movements

The target for eliciting tracking eye movements was a light spot, 3 cm in diameter, projected onto a screen placed 160 cm in front of the subject, and moving at various constant velocities of 10, 20, 30, 40, 50 or 60°/sec. The excursion of the target on the screen covered an amplitude of 60°. As soon as one target disappeared at the edge of the screen, the next one became visible at the opposite edge. At each velocity and direction, five trackings were recorded (Schalén, 1980).

Maximum velocity of smooth pursuit was measured on the part of the recording where smooth pursuit showed its highest velocity, lasting at least 250 msec and starting after an initial velocity adaptation period of 500 msec. The maximum velocity gain of smooth pursuit was calculated as the ratio maximum eye velocity/target velocity (Schalén, 1980).

Rotatory nystagmus

A rotatory test was conducted in a chair accelerated angularly to a constant velocity of $120^{\circ}/\text{sec}$ within 1 sec in the horizontal plane. After 60 sec the chair was brought to a standstill by a corresponding deceleration. This test was also carried out in the dark with the eyes open.

Statistics

The Mann-Whitney U-test was used to study the difference between normal values and values in patients concerning accuracy and reaction time of saccades. The left-right difference of these variables was tested with Wilcoxon's rank sum test. The statistical evaluation between peak velocity of saccades and smooth pursuit curves was made with a two-way analysis of variance with repeated test design. The results in the saccade test on time command were evaluated by using logistic models (Chatterjee & Price, 1977) and the differences in the coefficients in the logistic models were tested against t-distribution. The difference between samples was considered statistically significant when $p < 0.05$.

RESULTS

S a c c a d e s

Accuracy

The accuracy of the saccades was quantified and expressed by the amplitude of the initial saccades at the intended effort to produce a saccade of 60° . When compared with normal subjects the accuracy was significantly reduced in both directions in the patients ($p < 0.001$). There was no significant difference between saccadic accuracy to the right and to the left (Fig. 1).

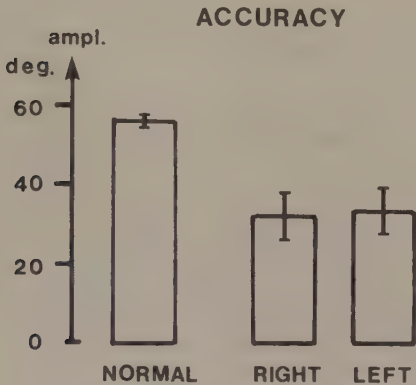


Fig. 1. Accuracy of voluntary saccades at an amplitude of 60° in 20 normal subjects and in patients with a frontal lobe lesion. For the patients, saccades to right and left are depicted. Means and standard error of mean are shown.

Latency

The latency period for saccades displayed highly variable responses. When compared with normal subjects their latency period was significantly increased in both directions ($p < 0.01$), though not symmetrically. Saccades directed towards the site of the lesion showed shorter latency periods than saccades away from it ($p < 0.01$) (Fig. 2).

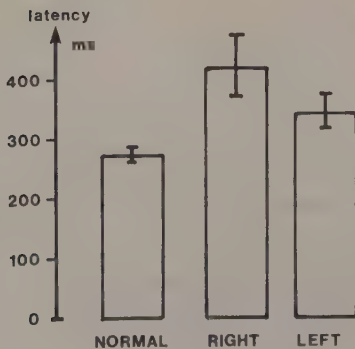


Fig. 2. Latency for 10 consecutive saccades at an amplitude of 60° in 20 normal subjects and in the patients with a frontal lobe lesion. For the patients, saccades to right and left are depicted. Means and standard error of mean are shown.

Saccades on time command

Efforts to produce saccades on time command varying from 1.2 sec to 0.4 sec revealed profound differences between patients and normal subjects. Most patients with a frontal lobe lesion showed great difficulties in programming their saccades according to the time command at intervals of one second or less. At this time interval, half of the patients were unable to make reflexional saccades in tact with the signal. At shorter intervals their ability was further disturbed and none of the patients could make reflexional saccades at a time interval of 0.4 sec (Fig. 3). The difference between normal subjects and patients was highly significant ($p < 0.001$).

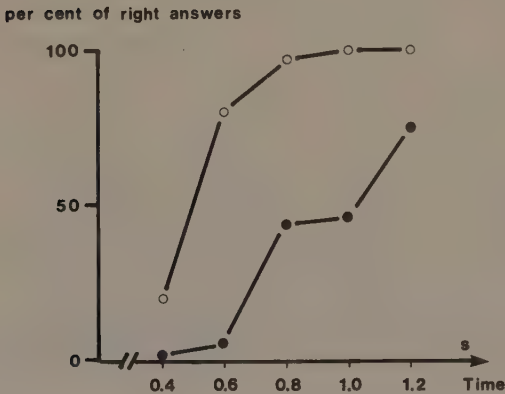


Fig. 3. Proportion of subjects responding with correct answer in saccadic test on time command. Upper curve (○) represents values gathered from 20 normal subjects. Lower curve (●) represents values received from the patients with a frontal lobe lesion. The time interval for command signal is indicated on the abscissa.

Velocity

The peak velocity of saccades was analysed with respect to amplitude (Fig. 4). The saccades directed towards the left had normal peak velocities, whereas saccades to the right had decreased velocity ($F(1.26) = 10.25$, $p < 0.01$).

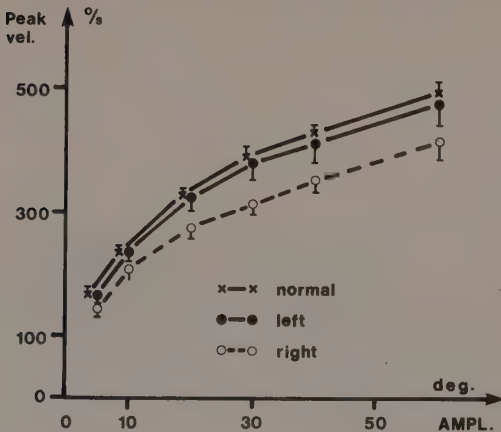


Fig. 4. Peak velocity curves of voluntary saccades at different amplitudes in 20 normal subjects and in the patients with a frontal lobe lesion. For the patients, saccades to right and left are depicted. Means and standard error of mean are shown.

Smooth pursuit

The maximum velocity gain of smooth pursuit was decreased in both directions, though to a various extent. The reduction of maximum velocity to the right was less disturbed, though still pathological ($p < 0.01$). ($F(1.28) = 13.59$, $p < 0.001$). The maximum velocity of smooth pursuit towards the left lesion was more defective. The difference in the maximum velocity between normal subjects and patients was highly significant ($F(1.28) = 36.83$, $p < 0.001$) (Fig. 5).

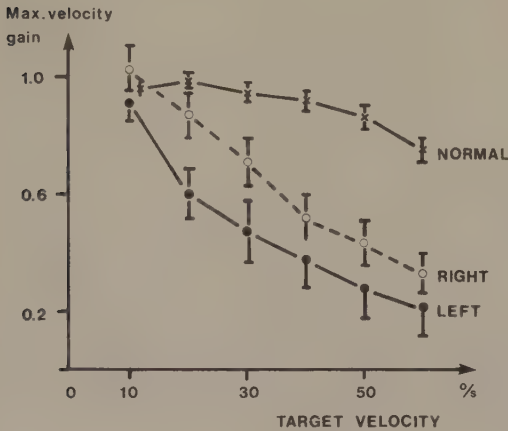


Fig. 5. Curves exhibiting maximum velocity gain of smooth pursuit at different target velocities in 20 normal subjects and in the patients with a frontal lobe lesion. For the patients, maximum velocity gain to right and left are depicted. Means and standard error of mean are shown.

Vestibular nystagmus

The velocity of the slow component of rotatory nystagmus showed a tendency to increase, when compared with normal subjects (Fig. 6), though the difference did not reach the level of statistical significance. Moreover, no statistically significant differences between rotatory responses to the right or to the left were observed.

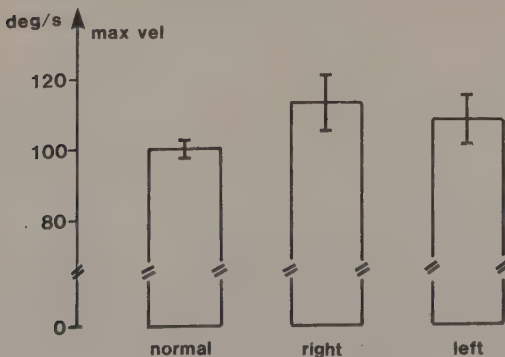


Fig. 6. Maximum velocity of angular acceleration induced nystagmus in 20 normal subjects and in the patients with a frontal lobe lesion. For the patients, responses to right and left are depicted. Means and standard error of mean are shown.

DISCUSSION

In this study of oculomotor performance of patients with speech dyspraxia all patients exhibited disturbances that could be ascribed to the underlying pathology of the left frontal lobe. Characteristically, the accurate movements of the eyes were replaced by more haphazard movements. The saccadic accuracy was reduced, the reaction time prolonged, and the execution of the saccades on time command was impaired. Similarly, the execution of the smooth pursuit eye movements was not so accurate, showing a reduced maximum velocity gain. The vestibular responses showed a tendency to hyperactivity. Many of the eye motor defects in these patients could be named "oculomotor dyspraxia", closely reminiscent of the speech dyspraxia.

1. Disturbance of initiation of eye movements

The role of the frontal eye field (FEF) in initiating saccades has been widely disputed, since Bizzi & Schiller (1970) and Mohler et al. (1973) were not able to observe any presaccadic activity in FEF. Instead, the neurons in FEF were activated during or after the saccades. Also, some of the neurons responded to smooth pursuit, nystagmus and head turning. Therefore, FEF has been proposed to control rather than to initiate the voluntary eye movements.

Recently, Goldberg & Bushnell (1981) showed that FEF in the monkey consists of at least three subpopulations of neurons, the vast majority of which were firing in connection with saccades. The burst activity preceded the saccades and was dependent on visual intention. These neurons did not burst prior to saccades when the visual target was absent or when the saccades were randomly spaced. Hence, the presaccadic activity of FEF seems to represent the neural events preceding purposeful, visually guided saccades.

The present results confirm the idea that FEF governs the preprogramming of voluntary eye movements. Consistently, the patients had profound difficulty in initiating voluntary eye movements. The initiation of the saccades was disturbed, with prolonged reaction times. Moreover, the saccades appeared more or less at random, indicating a lack of voluntary control over these movements.

2. Does a unilateral frontal lobe lesion cause unilateral or bilateral oculomotor deficits?

Unilateral electrical stimulation of the FEF causes conjugated deviation of the eyes to the contralateral hemifield (Penfield & Rasmussen, 1950). Depending on the strength of the stimulation current, saccades or smooth pursuit are evoked (Robinson & Fuchs, 1969). In monkey, a lesion in FEF produces temporary visual neglect and inaccuracy in fixating in the contralateral

hemifield (Latto & Cowey, 1971; Schiller et al., 1980). In man, quantitative studies on the oculomotor function after a lesion in FEF have not been carried out in detail and the consequences of lesions have not been conclusive (cf. Crowne et al., 1981).

In several oculomotor tests in the present study we found significant left-right differences. For example, the reaction time was significantly prolonged in the saccades directed to the contralateral hemifield, when compared with ipsilateral saccades. The peak velocity of the saccades tended to be reduced when directed contralaterally to the lesion. Smooth pursuit was reduced ipsilaterally to the lesion. It was remarkable that these differences existed even in 3 subjects who had bilateral hemispherical lesions. These findings support a laterality of the supratentorial regulation of the oculomotor system. However, in several oculomotor tasks eye movements were disturbed in both directions when compared with normal subjects. Thus, the saccades were equally inaccurate to right and to left, and the latency was also reduced in saccades ipsilateral to the lesion. The bilateral reduction persisted even when the 3 patients with cerebral atrophy were excluded from the analysis.

Confirming the possibility of a bilateral oculomotor involvement of unilateral lesions in FEF, the neural population in FEF is not strictly unilateral since there is a significant representation from ipsi- and contralateral eye movements (Goldberg & Bushnell, 1981). Furthermore, Liepmann (1913) noticed that patients with left hemisphere damage demonstrated ipsilateral and contralateral deficits during limb apraxia tasks. He concluded that the left hemisphere was more important for the control of skilled motor movements than was the right hemisphere, which has been demonstrated in a wide variety of tests of limb apraxia (Geschwind, 1975). Moreover, in a recent study Haaland & Delaney (1981) confirmed the bilateral deficits in motor performance in patients with a unilateral frontal lobe lesion. However, the ipsilateral deficits occurred in their study to approximately the same extent irrespective of the extent and origin of the lesion or whether the lesion was located in the dominant or non-dominant hemisphere. The conceivable dominance of the left hemisphere in the ocular movement cannot be deduced from the present results.

3. Accuracy of saccades and frontal lobe lesions

An animal deprived of its frontal lobes is unable to analyse and correct its inadequate motor reactions (Pribram et al., 1964). Correspondingly, the subjects in this study exhibited difficulties in executing saccades of correct spatial distance. Instead of reaching the target with one accurate saccade, the subjects conducted saccades in a trial and error manner, exhibiting "a staircase pattern" of hypometric saccades. This disturbed pattern may be the result of an impaired ability to organize the motor act by the lesioned prefrontal cortex.

The difficulties experienced in the saccadic test may also arise through visual perception. Impaired perception in connection with a FEF lesion is reflected as visual neglect (Latto & Cowey, 1971). Normally, visual neglect becomes rapidly compensated for. Since the majority of our patients were elderly and suffered from vascular or degenerative lesions, their capacity to compensate for the lesion was limited. Dysfunction may be lasting and cause reduced visual explorative function in these patients.

The vast majority of the saccades under normal conditions are limited between 5 and 15° (Collewyn, 1977). If saccades larger than these are needed, turning of the head will assist the movement of the eyes. The disturbances in accuracy may be the result of difficulties in exposing the oculomotor system to such a novel task as executing saccades at 60°. Thus, by encouraging the subjects to perform large saccades in our test we may expose them to a novel experience in which the subject may continue to perform the memorized pattern of eye movements. This kind of movement perseveration in frontal lobe lesions (Brody & Pribram, 1978) may, in fact, be the reason why the goal-directed saccades were small yet persistent in these patients.

4. Time control of saccades and frontal lobe lesion

In the preprogramming of the voluntary saccades, anticipation and timing of the different movement sequences, i.e. determination of the extent of activation of agonistic extraocular muscles and relaxation of the antagonistic extraocular muscles within the time frame, is critical. If the time concept becomes faulty, pacing of individual eye movement sequences will fail. Saccades will show a certain inaccuracy, retardation or increase in reaction time. All these findings were observed in the present study.

The most striking finding among the subjects was, however, the inability to perform saccades according to time command. It was noteworthy that 3 out of 10 patients could not perform this task even within longest time interval, viz. 1.2 sec. Since the reaction time for the saccades in these subjects was less than 0.8 sec, a prolonged reaction time could not fully explain this finding. Moreover, the time command task specifically requires anticipation of the target shift. Our findings are in agreement with those of Brody & Pribram (1978) who showed that patients with frontal lobe lesions have the greatest difficulty in performing tasks where temporal organization of motor performance is required.

5. Disturbance in smooth pursuit

Consistent with earlier concepts (Troost et al., 1972) we found a reduction in velocity of smooth pursuit contralateral to the lesion. This finding supports the idea, based on neuroanatomical studies (Brodal, 1978), that smooth pursuit exhibits a contralateral dominance. Smooth pursuits are

executed to a great extent by prediction (Fleming et al., 1969). Hence, the impaired capacity may be ascribable to the lesion of the neural mechanisms controlling memorized movements (Geschwind, 1975; Eccles, 1982).

Nevertheless, smooth pursuit requires visual attentiveness. Deficit in attention span, commonly met with in disorders of the prefrontal cortex (Fuster, 1980), may contribute to the reduced velocity. Patients with a frontal lobe lesion face difficulties when concentrating and new irrelevant causes may easily disperse their attention.

6. Hyperactivity of vestibular responses

In the present study we found that the vestibular responses tended to be hyperactive. This observation is supported by earlier experimental studies. When certain parts of the premotor area are stimulated, movements become depressed and muscle tonus will be less tense (cf. Luria, 1980). This suggests that the premotor area depresses the reflex motor activity in the brain stem. A lack of this function following a lesion will enhance primitive reflexes, as observed in this study.

CONCLUSION

In patients with a frontal lobe lesion, exhibiting speech dyspraxia, the oculomotor performance was disturbed. The saccades showed increased reaction time, decreased accuracy and contralateral reduced peak velocity. The difficulties in releasing the saccades when tried to perform saccadic task on time command were striking. The smooth pursuit was reduced in maximum velocity gain. The vestibular responses showed a tendency to be hyperactive. The finding can be attributed to a dysfunction of the frontal lobe, leading to difficulties in preprogramming and execution of oculomotor tasks.

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